HEART FAILURE IN YOUNG ADULTS

by

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List of abbreviations

ACE	angiotensin converting enzyme
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
BMI	body mass index
BNP	brain natriuretic peptide
BP	Blood pressure
CABG	coronary artery bypass graft
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CPRD	Clinical Practice Research Datalink
CRT	cardiac resynchronisation therapy
DCM	Dilated cardiomyopathy
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
HF	heart failure
HF-PEF	heart failure with preserved ejection fraction
HF-REF	heart failure with reduce ejection fraction
ICD	implantable cardioverter defibrillator
LV	left ventricle
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVM	left ventricular mass
MAGGIC	Meta-analysis Global Group in Chronic heart failure
NT-pro BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association functional class
VAD	ventricular assist device

Summary

Heart failure (HF) is a major health concern affecting 15 million people in Europe and around 900 000 people in the U.K. HF predominantly affects the elderly, with the mean age of patients with a diagnosis of HF between 70 and 80 years. Most previous HF studies have accordingly focused on older patients. Although HF is less common in younger adults (<65 years), 15% to 20% of patients hospitalised with HF are younger than 60 years of age. Very few studies have described the characteristics of younger adults with HF and its outcome.

The aims of this thesis are to describe the clinical characteristics of younger adults with HF, explore the epidemiology of HF in younger adults and determine their short- and long-term outcomes. This was made possible by access multiple databases consisting of large patient cohorts with HF. The first chapter is a systematic literature review of younger adults with HF. Gaps in the current literature were identified and the thesis focused on some of these.

The CHARM study allows detail characterisations of younger adults with HF. It recorded characteristics of patients with HF, including symptoms and signs of HF, electrocardiographic changes, chest radiographic findings, and also left ventricular ejection fraction. HF hospitalisations and its precipitating factors were also recorded systematically. Younger adults were more likely to have a third heart sound and hepatomegaly, but less likely to have pulmonary crackles and peripheral oedema. Similarly, radiological findings in younger adults were less likely to show interstitial pulmonary oedema or pleural effusion. Interestingly, younger adults aged <40 years not only have similar HF hospitalisation rate to older patients, however during their presentation with decompensated HF, they were less likely to have clinical pulmonary oedema and radiological signs of HF. Physicians managing younger adults with HF need to be aware of this. Younger adults were also less compliant with medications and lifestyle restriction resulting in hospitalisation with decompensated HF. Fortunately, despite these challenges, mortality rates in younger adults with HF were lower compared to older patients.

To further substantiate the findings from the CHARM study, the MAGGIC study, a meta-analysis consists of over 40 000 patients with HF from large observational studies and randomised controlled trials, was examined. In both databases, the commonest aetiology of HF in younger adults was dilated cardiomyopathy. The ejection fraction was the lowest in younger adults. Similar to the CHARM study, mortality rates in younger adults were lower compared to older patients. However, in the MAGGIC study, by stratifying mortality into patients with preserved ejection fraction and with reduced ejection fraction, younger patients with preserved ejection fraction have a much lower mortality rate compared to patients with reduced ejection fraction.

Findings from clinical trials are not always reflective of the real life clinical practice. The U.K. Clinical Practice Research Datalink (CPRD), a large and well-validated primary care database with 654 practices contributing information into the database representing approximated 8% of the U.K. population, is a rich dataset offering a unique opportunity to examine the characteristics, treatments, and outcomes of younger adults with HF in the community. In contrast to the CHARM and MAGGIC studies, younger adults aged <40 years were stratified into 20-29 and 30-39 years in the CPRD analysis. This is possible due to the larger number of younger adults with HF. Further stratifying the younger age groups demonstrated heterogeneity among younger adults with HF. In contrast to previous data showing younger adults have lower comorbidities, the proportions of depression, chronic kidney disease, asthma, and any connective tissue disease were high among patients aged 20-29 years in the analysis from the CPRD. Surprisingly, the treatment rates for angiotensin converting enzyme (ACE) inhibitor, and aldosterone antagonist were the lowest in patients aged 20-29 years. With the exception of patients aged ≥80 years, treatment rate with beta-blocker was also the lowest in patients aged 20-29 years. With over two decades of follow up, long-term mortality rates in younger adults with HF can be determined. The mortality rates continued to decline from 1988 to 2011. Physicians managing younger adults with HF can now use this contemporary data to provide prognostic information to patients and their family.

A hospital administrative database is the logical next platform to explore younger adults with HF. The Alberta Ministry of Health database links an outpatient database to a hospitalisation database providing ample data to examine the relationship between

outpatient clinic visits and hospital admissions in younger adults with HF. Following a diagnosis of HF in the outpatient setting, younger adults were admitted to the hospital with decompensated HF much sooner than older patients. Younger adults also presented to emergency department more frequently following their first hospitalisation for HF.

In conclusion, this thesis presented the characteristics and outcomes of younger adults with HF, and helped to extend our current understanding on this important topic. I hope the data presented here will benefit not only physicians looking after younger adults with HF, but also patients and their family.

Chapter 1

Introduction

A review of the epidemiology, and characteristics of young adults with heart failure

1.1 Background

Heart failure (HF) affects around 900,000 people in the UK and 15 million people in Europe.(1;2) Approximately 20% of hospitalised patients with HF are less than 65 years of age.(3) Most studies have focussed on the elderly. Little attention has been given to young adults with HF until recently. An improved understanding of the epidemiology, outcomes, and aetiology of young adults with HF may help managing these patients. I conducted a literature review to evaluate the current understanding of HF in young adults.

1.1.1 Definition of HF

The U.K. National Institute for Health and Care Excellence defines HF as a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is caused by structural or functional abnormalities of the heart.(4) Similarly, the European Society of Cardiology defines HF as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolising tissues, despite normal filling pressures or in the expense of increased filling pressure.(5)

Prior to these authoritative definitions, HF was broadly defined as an inability of the heart to pump blood around the body to meet its metabolic demands resulting in a clinical syndrome characterised by a constellation of symptoms and signs.(6)

1.1.2 Definition of young

In the U.K. cardiac transplant is rarely performed in patients aged 65 years and above with end-stage HF.(7) Young is, therefore, pragmatically defined as adults less than 65 year of age. Patients aged <40 years are arbitrary defined as very young adults.

1.2 Search strategy

English language publications in *Pubmed, EMBASE and Cochrane Library* from 1966 to January 2014 were searched. The search combined terms related to HF: 'heart failure', 'ventricular dysfunction', 'systolic dysfunction', 'myocardial failure' and 'cardiac failure' with generic terms 'epidemiology', 'incidence', 'prevalence', 'mortality', 'hospitalisation', 'aetiology', 'etiology', 'young' and 'age' using Boolean operators. A hand search of references identified from articles was conducted. The search was performed by myself and another researcher independently. Data from studies meeting the search criteria were entered into pre-defined tables independently. Only studies defined young as less than 65 years of age or younger were selected. For studies reporting mortality in patients with HF, I have only selected studies reporting mortality rates from year 2000 onwards.

1.3 Epidemiology

1.3.1 Incidence of HF in young adults with HF

The incidence of HF in young and very young adults is low. In Europe and the US incidence of HF in those aged < 65 years is 0.40 per 1000 population per year in comparison to 5.80 to 7.30 per 1000 population per year in those aged ≥65 years (Table 1.1).(8;9) Only one study has been performed outside Europe or North America in Taiwan. There are limited data on incidence of HF in very young adults (two from the UK, two from France, and one from Taiwan). The incidence of HF (per 1000 population per year) in the UK ranges from 0.00 to 0.02 in 25 to 34 years, 0.00 to 0.20 in 35-44 years, 0.08-0.38 in 45-54 years, and 0.64 to 1.70 in 55-64 years.(8;9) This is similar to other studies performed in Europe and Taiwan: 0.02 per 1000 population in age group 20 to 30 years and 0.26 per 1000 population in age group 20 to 44 years, respectively.(10;11)

The studies from the UK are over a decade ago and those from France or Taiwan were based on hospitalisation data. More contemporary study examining incidence of HF in primary care and secondary care is needed.

1.3.2 Trends in incidence of HF in young adults with HF

The incidence of HF in young adults with HF remains static in the last three decades.

Data from Western Australia (1990 to 2005) and the UK (1984 to 1992 and 1993 to 2001) demonstrated that the incidence HF hospitalisation in younger adults (<65 years) has not change significantly since the mid 80's (Table 1.2).(12-14) The relative percentage change (2002-2005 vs. 1990-1993) of the age standardised rates of index hospitalisation for HF in patients aged <65 years was +1.70% (27.47 per 100000 vs. 27.00 per 100000) in men and -11.50% (14.93 per 100000 vs. 16.87 per 100000) in women.(12) A recent Swedish study included all patients with a primary or secondary diagnosis of HF from the Stockholm regional health care data which contains all consultations in primary and secondary (defined as specialist outpatient care) care, and all hospitalisations showed incidence of HF between 2006 and 2010 remains static in age groups 40-49 and 50-59 years while the incidence in those aged >60 years decreases.(15) Similarly, a study from Australia reporting index admission for HF by age group demonstrated little change in the rates of index admission for HF between 2002-2003 and 2006-2007 in patients <65 years compared to those aged ≥65 years which index admission rates have been decreasing over time.(16)

Another study from Sweden included patients with first-ever HF diagnosis code in any position from the national hospital discharge registry reported the incidence of HF from 1987 to 2006 increased by 50% (2.5 per 100000 in 1987-1991 to 3.7 per 100000 in 2002-2006) and 43% (10.2 per 100000 in 1987-1991 to 14.6 per 100000 in 2002-2006) among individuals aged 18-34 and 35-44 years, respectively.(17)

Among these studies, only two studies (one from the Sweden, and one from Scotland) included very young adults with HF showing conflicting trends of incidence of HF. More studies in the very young adults and also from other countries would help to confirm these results.

Table 1.1: Incidence of HF by country, and gender in young adults with HF

Location	Year	Type of study	Number	Incidence (per 1000/year)			
U.K.							
Scotland(18)	1999 to 2000	Retrospective, primary care cohort study	307741		Men	Women	Total
				45-64	1.40	1.30	1.30
				65-74	6.00	6.10	6.10
				75-84	20.20	13.50	16.00
				≥85	24.80	21.60	22.40
				Total	1.80	2.20	2.00
Bromley, South London(8)		Population cohort study	292000		Men	Women	
				25-34	0.00	0.00	
				35-44	0.04	0.00	
				45-54	0.38	0.08	
				55-64	1.71	0.64	
				65-74	3.30	1.74	
				75-84	8.10	5.45	
				≥85	10.44	5.99	
				>24	1.40	1.10	
UK GPRD(19)	1996	Retrospective, primary care cohort study	689467		Men	Women	
				40-44	0.24	0.16	
				45-49	0.72	0.11	
				50-54	0.70	0.32	
				55-59	2.13	0.85	
				60-64	4.47	2.43	
				65-69	6.38	4.59	
				70-74	11.28	7.86	
				75-79	19.24	15.48	
				80-84	31.17	22.09	
Hillingdon(9)	1995 to 1996	Population cohort study	151000		Men	Women	Total
				25-34	0.00	0.04	0.02
				35-44	0.20	0.20	0.20
				45-54	0.30	0.10	0.20
				55-64	1.70	0.70	1.20
				65-74	3.90	2.30	3.00
				75-84	9.80	5.90	7.40
				85+	16.80	9.60	11.60
UK GPRD(20)	1991 to 1994	Retrospective, primary care cohort study	696884	55-64	3.40		
				75-84	25.50		
UK GP(21)	1991 to 1992	Retrospective national database	-		Men	Women	Total
				45-64	1.40	1.00	1.00
				65-74	9.30	7.40	8.30
				75-84	22.70	16.20	18.60
				85+	29.10	32.90	32.00
				Overall			2.30
Other European countries							
France (110)	2009	Retrospective, hospitalised cohort study	69958		Men	Women	Total
				20-39	-	-	-
				40-49	<1.00	<1.00	<1.00
				50-54	1.00	<1.00	<1.00
				55-59	1.00	<1.00	1.00
				60-64	2.00	1.00	1.00
				65-69	3.00	2.00	2.00
				70-74	5.00	3.00	4.00
				75-79	9.00	6.00	7.00
				80-84	16.00	11.00	12.00
				85-89	26.00	19.00	21.00
				90-94	34.00	28.00	30.00
				95+	37.00	33.00	34.00
Goteborg(22)	1970 to 1996	Population cohort study	7495		Men		
				55-64	2.10		
				65-74	9.10		
				75-79	11.50		

Groningen(23)	1993 to 1998	Population cohort study	5279		Men		Women
				57-60	2.50		2.50
				61-69	6.40		4.10
				70-79	20.00		15.40
				80+	28.20		22.40
Lorraine, France(11)	1994	Prospective, hospitalised with advanced heart failure, cohort study	499		Men	Women	Total
				20-30	0.02	0.01	0.02
				30-40	0.02	0.02	0.02
				40-50	0.16	0.02	0.09
				50-60	0.47	0.07	0.27
				60-70	0.98	0.28	0.60
				70-80	1.48	0.58	0.94
Rotterdam(24)	1989 to 1993	Population cohort study	7983	55-59	1.40		
				60-64	3.10		
				65-69	5.40		
				70-74	11.70		
				75-79	17.00		
				80-84	30.10		
				85-89	41.90		
				≥90	47.40		
Eastern Finland(25)	1986 to 1988	Prospective, community cohort study	11000		Men		Women
				Boston criteria			
				45-54	1.90		--
				55-64	3.10		1.50
				65-74	8.20		2.00
				45-74	3.60		1.10
				Framingham criteria			
				45-54	2.30		0.20
				55-64	3.30		2.20
				65-74	7.70		2.90
				45-74	3.80		1.70
U.S.							
Forsyth County, Jackson, suburbs of Minneapolis, Washington County(26)	1987 to 2002	Population cohort study	15792		Men		Women
				Caucasian			
				45-49	2.40		1.70
				50-54	5.60		3.10
				55-59	8.40		4.40
				60-64	14.30		7.70
				African American			
				45-49	5.20		3.80
				50-54	7.20		7.60
				55-59	14.00		10.10
				60-64	13.40		17.40
Worcester(27)	2000	Retrospective, hospitalised cohort study	2604	<55	0.31		
				55-64	1.81		
				65-74	4.23		
				75-84	11.00		
				≥85	18.20		
Framingham(28)	40 years follow up	Population cohort study	-		Men		Women
				45-54	2.00		1.00
				55-64	5.00		3.00
				65-74	10.00		8.00
				75-84	19.00		14.00
				85-94	28.00		26.00
Rochester(29)	1981 to 1982	Retrospective, population cohort study	-		Men		Women
				45-49	1.00		0.00
				50-54	1.00		0.00
				55-59	3.00		1.00
				60-64	6.00		2.00
				65-69	16.00		5.00
				70-74	9.00		10.00
				0-74	1.60		0.70
Others							
Taiwan(10)	2005	Retrospective, hospitalised cohort study	1 million		Men	Women	Total
				20-44	0.39	0.15	0.26
				45-54	1.57	0.96	1.27
				55-64	4.28	2.74	3.49
				65-74	13.10	11.24	12.15

≥75	33.14	38.09	35.52
20-64	1.14	0.64	0.88
≥65	21.70	21.92	21.81
All	3.91	3.37	3.63

Table 1.2: Trends of incidence of HF by country, gender, and year in young adults with HF

Location	Year	Type of study	Number	Incidence (per 1000 population/year)		
Sweden(15)	2006-2010	Cross sectional study	2.1 million		Men	Women
				2006		
				40-49	0.60	0.30
				50-59	2.40	1.10
				60-69	7.00	3.50
				70-79	19.10	14.40
				80-89	43.40	35.20
				≥90	71.70	57.40
				2007		
				40-49	0.60	0.30
				50-59	2.20	1.20
				60-69	5.80	3.40
				70-79	17.50	14.20
				80-89	41.10	34.80
				≥90	62.60	52.90
				2008		
				40-49	0.60	0.30
				50-59	2.10	1.00
				60-69	5.70	3.10
				70-79	16.80	12.60
				80-89	42.60	35.00
				≥90	60.30	49.60
				2009		
				40-49	0.60	0.20
				50-59	2.20	0.80
				60-69	4.80	2.90
				70-79	14.90	12.00
				80-89	39.50	34.60
				≥90	56.40	51.40
				2010		
				40-49	0.50	0.20
				50-59	2.10	1.00
				60-69	5.20	2.30
				70-79	13.20	10.70
				80-89	38.20	31.00
				≥90	51.50	42.50
Australia(16)	2000-2007	Retrospective, hospitalised cohort study (first index HF hospitalisation)		age	Men	Women
				2002-2003		
				45-49	0.19	0.10
				50-54	0.34	0.19
				55-59	0.71	0.38
				60-64	1.33	0.76
				65-69	2.36	1.52
				70-74	4.14	3.12
				75-79	6.92	4.94
				80-84	11.65	8.87
				85+	19.50	14.31
				2003-2004		
				45-49	0.16	0.10
				50-54	0.37	0.26
				55-59	0.65	0.37
				60-64	1.56	0.79
				65-69	2.26	1.48
				70-74	4.33	2.72

				75-79	6.78	4.86
				80-84	10.93	8.00
				85+	18.65	16.03
				2004-2005		
				45-49	0.15	0.08
				50-54	0.31	0.17
				55-59	0.65	0.31
				60-64	1.32	0.65
				65-69	2.38	1.40
				70-74	3.92	2.50
				75-79	6.20	4.66
				80-84	10.27	7.93
				85+	17.81	13.94
				2005-2006		
				45-49	0.28	0.09
				50-54	0.41	0.17
				55-59	0.63	0.34
				60-64	1.37	0.61
				65-69	2.12	1.16
				70-74	3.58	2.47
				75-79	6.87	4.42
				80-84	10.58	7.29
				85+	18.71	14.94
				2006-2007		
				45-49	0.21	0.12
				50-54	0.39	0.16
				55-59	0.67	0.35
				60-64	1.31	0.62
				65-69	1.90	1.19
				70-74	3.46	2.67
				75-79	6.53	4.20
				80-84	11.33	7.75
				85+	17.85	14.96
Sweden(17)	1987 to 2006	Population cohort study	443995		Men	Women
				1987-91		
				18-34	0.03	0.02
				35-44	0.13	0.07
				45-54	0.63	0.29
				55-84	9.47	5.22
				1992-96		
				18-34	0.03	0.02
				35-44	0.17	0.10
				45-54	0.80	0.39
				55-84	10.98	6.31
				1997-2001		
				18-34	0.03	0.03
				35-44	0.16	0.09
				45-54	0.78	0.33
				55-84	8.96	4.99
				2002-06		
				18-34	0.04	0.03
				35-44	0.19	0.10
				45-54	0.74	0.31
				55-84	7.77	4.36
Georgia(30)	2000 to 2005	Retrospective, hospitalised and outpatient cohort study	359947		Men	Women
				2000		

				18-54	1.36	0.97
				55-64	6.76	7.29
				65-74	27.24	22.23
				≥75	55.25	56.40
				2001		
				18-54	1.48	1.18
				55-64	10.47	7.53
				65-74	24.56	20.14
				≥75	56.07	56.34
				2002		
				18-54	1.56	1.33
				55-64	11.83	6.91
				65-74	24.79	22.98
				≥75	49.01	52.81
				2003		
				18-54	1.34	1.32
				55-64	9.21	5.86
				65-74	25.15	18.21
				≥75	57.13	44.19
				2004		
				18-54	1.55	1.11
				55-64	8.78	6.54
				65-74	26.09	16.36
				≥75	40.40	42.14
				2005		
				18-54	1.22	0.91
				55-64	8.95	5.48
				65-74	18.49	15.57
				≥75	57.83	41.39
Western Australia(12)	1990 to 2005	Retrospective, hospitalised cohort study	19342		Men	Women
				1990-1993		
				<65	0.27	0.17
				65-74	4.26	2.85
				≥75	12.87	10.38
				1994-1997		
				<65	0.27	0.15
				65-74	3.44	2.31
				≥75	10.11	8.18
				1998-2001		
				<65	0.24	0.15
				65-74	2.84	1.94
				≥75	8.66	7.05
				2002-2005		
				<65	0.28	0.15
				65-74	2.38	1.52
				≥75	7.80	6.32
				Relative % change		
				<65	+1.7	-11.5
				65-74	-44.1	-46.5
				≥75	-39.4	-39.0
Scotland(14)	1984, 1988, and 1992	Retrospective, hospitalised cohort study	5.1 million		Men	Women
				1984		
				<25	0.02	0.01
				25-54	0.34	0.17
				55-64	3.17	1.78
				65-74	8.12	5.15
				>75	18.08	14.51
				1988		
				<25	0.03	0.02
				25-54	0.32	0.17
				55-64	3.33	1.90
				65-74	8.04	5.27
				>75	18.43	15.00
				1992		
				<25	0.03	0.03
				25-54	0.40	0.20
				55-64	3.92	2.15
				65-74	9.99	6.36
				>75	22.08	18.86

1.3.3 Prevalence of HF in young adults with HF

The prevalence of HF in very young adults (<40 years) is low ranging from 0.01-0.30% (Table 1.3).(31-33) In adults aged 45-54 years and 55-64 years, the prevalence of HF range from 0.13-1.30% and 0.52-5.50%, respectively.(34-36) Between 1980 and 1998, some studies reported similar prevalence of HF in younger adults over two decades (approximately 0.01%) in young adults aged 0-34 years and 25-44 years.(37;38) Another study utilised the electronic medical record system of Kaiser Permanente reported prevalence of HF in patients aged 18-54 years and 55-64 years increased by about a third from 2000 to 2005 (men vs. women: 18-54 years: 0.41% vs. 0.34% in 2000 and 0.60% vs. 0.52% in 2005; 55-64 years: 3.35% vs. 2.41% in 2000 and 4.64% vs. 3.17% in 2005).(30) Between 2006 and 2010, the prevalence of HF remained unchanged.(15) Very little is known about the prevalence of HF in the rest of the world.

1.3.4 Prevalence of left ventricular systolic dysfunction (LVSD) in young adults with HF

The definition of LVSD varies between studies limiting inter-study comparison. The Framingham Study defined LVSD as ≤50%(39); a Scotland study as ≤30%(40); the Echocardiographic Heart of England screening study as <40%(34), and the Harrow Heart Failure Watch Study as <45%(41).

The prevalence of asymptomatic LVSD in young adults is 0.0% in 25-34 years, 0.35% in 35-44 years, 2.8% in 45-54 years and 1.6% in 55-64 years.(40)

Table 1.3. Prevalence of heart failure by country, and gender in young adults with HF

Location	Year	Type of study	Number	Prevalence (%)			
U.K.							
Kent, Surrey and Sussex(33)	2002 to 2003	Population-based cohort study	256188		Men	Women	Total
				0-34	0.02	0.01	0.02
				35-44	0.02	0.03	0.03
				45-54	0.11	0.06	0.09
				55-64	0.56	0.33	0.44
				65-74	2.37	1.52	1.92
				75-84	6.82	6.09	6.38
				85+	12.57	12.47	12.5
				All age	0.71	0.95	0.83
Harrow(41)	2000 to 2001	Population-based cohort study	734	Prevalence of LVSD <45%			
					Men	Women	Total
				45-54	2.50	0.00	1.10
				55-64	3.30	1.60	2.30
				65-74	10.80	0.00	6.30
				75-84	11.40	2.90	7.10
				≥75	13.20	7.10	10.00
Scotland(18)	1999 to 2000	Retrospective, primary care-based cohort study	307741		Men	Women	Total
				45-64	0.43	0.32	0.38
				65-74	2.57	2.07	2.30
				75-84	6.39	5.31	5.73
				≥85	10.39	8.52	9.01
				Total	0.64	0.78	0.71
West Midland(34)	1995 to 1999	Population-based cohort study	3960		Men	Women	Total
				Definite HF according to ESC criteria			
				45-54	0.30	0.00	0.20
				55-64	2.70	0.90	1.80
				65-74	4.20	1.70	2.90
				75-84	7.30	6.60	6.90
				≥85	21.70	11.60	15.20
				Total	3.00	1.70	2.30
				LVEF <40%			
				45-54	0.60	0.00	0.30
				55-64	3.00	0.50	1.80
				65-74	4.80	1.10	2.90
				75-84	4.90	2.60	3.70
				≥85	8.70	0.00	3.00
				Total	3.00	0.70	1.80
				LVEF 40-50%			
				45-54	1.30	1.30	1.30
				55-64	4.00	3.00	3.50
				65-74	6.70	2.80	4.70
				75-84	6.30	5.70	6.00
				≥85	13.00	14.00	13.60
				Total	4.10	4.10	3.50
England and Wales(37)	1994 to 1998	Retrospective, primary care-based cohort study	1.4 million		Men	Women	
				1994			
				0-34	0.01	0.01	
				35-44	0.04	0.04	
				45-54	0.24	0.17	
				55-64	1.45	0.96	
				65-74	4.67	3.77	
				75-84	11.42	10.56	
				85+	18.41	20.23	

				1995		
				0-34	0.01	0.01
				35-44	0.04	0.03
				45-54	0.26	0.16
				55-64	1.46	0.97
				65-74	4.57	3.69
				75-84	11.20	10.25
				85+	18.41	19.72
				1996		
				0-34	0.01	0.01
				35-44	0.05	0.03
				45-54	0.28	0.17
				55-64	1.49	0.98
				65-74	4.48	3.67
				75-84	10.90	10.09
				85+	18.36	19.16
				1997		
				0-34	0.01	0.01
				35-44	0.04	0.03
				45-54	0.26	0.17
				55-64	1.44	0.94
				65-74	4.59	3.64
				75-84	11.01	10.05
				85+	18.29	18.59
				1998		
				0-34	0.01	0.01
				35-44	0.04	0.03
				45-54	0.27	0.18
				55-64	1.39	0.92
				65-74	4.49	3.58
				75-84	10.86	9.86
				85+	19.07	18.88
West London(42)	1997 to 1998	Retrospective, primary care-based cohort study	-	<65	0.10	
				65+	4.50	
Liverpool(43)	1994	Retrospective, primary care-based cohort study	151000		Men	Women
				35-44	0.00	0.10
				45-54	0.50	0.60
				55-64	2.20	1.10
				65-74	3.90	4.50
				75+	4.10	9.60
Scotland(40)	1992	Cross sectional survey	1640		Men	Women
				Symptomatic HF with EF≤30%		
				25-34	0.00	0.00
				35-44	0.00	0.00
				45-54	1.40	1.20
				55-64	2.50	2.00
				65-74	3.20	3.60
				Asymptomatic HF with EF≤30%		
				25-34	0.00	0.00
				35-44	0.70	0.00
				45-54	4.40	1.20
				55-64	3.20	0.00
				65-74	3.20	1.30
Nottingham(44)	1991 to 1992	Retrospective, primary care-based cohort study	22117	30-39	0.10	
				40-49	0.15	
				50-59	0.55	
				60-69	1.72	
				70-79	4.18	
				80-89	4.69	
				90+	5.45	
Scotland(38)	1980 to 1990	Retrospective, hospitalised-based cohort study	5.1 million		Men	Women
				1980		
				25-44	0.01	0.01
				45-64	0.15	0.09
				65-74	0.61	0.37
				75+	1.28	1.07
				Total	0.13	0.13

				1990			
				25-44	0.02	0.01	
				45-64	0.26	0.13	
				65-74	0.88	0.54	
				75+	1.91	1.53	
				Total	0.21	0.21	
North west London, Middlesex(45)	1988	Cross-sectional, primary care-based study	30204	<65	0.06		
				65+	2.77		
Other European countries							
Sweden(15)	2006-2010	Cross sectional study	2.1 million		Men	Women	
				2006			
				40-49	0.30	0.10	
				50-59	1.10	0.50	
				60-69	3.60	1.60	
				70-79	10.00	6.40	
				80-89	21.40	17.93	
				≥90	36.90	33.00	
				2007			
				40-49	0.30	0.10	
				50-59	1.10	0.50	
				60-69	3.40	1.50	
				70-79	9.60	6.40	
				80-89	21.20	17.90	
				≥90	34.30	32.70	
				2008			
				40-49	0.30	0.20	
				50-59	1.20	0.50	
				60-69	3.30	1.50	
				70-79	9.20	6.20	
				80-89	21.50	18.30	
				≥90	32.70	30.90	
				2009			
				40-49	0.30	0.20	
				50-59	1.20	0.50	
				60-69	3.10	1.50	
				70-79	8.70	6.00	
				80-89	21.60	18.20	
				≥90	33.00	31.80	
				2010			
				40-49	0.30	0.20	
				50-59	1.20	0.50	
				60-69	3.10	1.40	
				70-79	8.20	5.80	
				80-89	21.60	18.20	
				≥90	30.30	29.40	
Madrid(32)	2007	Cross-sectional, observational study	198670		Men	Women	Total
				<40	0.03	0.03	0.03
				40-49	0.06	0.08	0.07
				50-59	0.33	0.25	0.29
				60-69	0.99	0.70	0.83
				70-79	2.97	2.70	2.81
				>80	8.21	7.19	7.51
				ALL	0.59	0.79	0.69
Spain(35)	2004 to 2005	Population-based cohort study	1776		Men	Women	Total
				45-54	1.30	1.20	1.30
				55-64	7.40	3.60	5.50
				65-74	7.00	8.80	8.00
				>75	15.60	16.40	16.10
				Total	6.50	7.00	6.80
Dutch(36)	2001	National Survey in General Practice	374000		Men	Women	Total
				0-24	<0.01	<0.01	<0.01
				25-44	0.02	0.02	0.02
				45-54	0.14	0.12	0.13
				55-64	0.75	0.31	0.52
				65-74	2.63	1.77	2.17
				75+	9.67	8.56	9.17
				ALL	0.67	0.81	0.74
Madeira(46)	2000 to	Prospective, cross-sectional,	686	25-49	1.24		

	2001	observational study		50-59	6.17		
				60-69	7.62		
				70-79	13.32		
				80+	14.34		
Rotterdam(24)	1989 to 2000	Population-based cohort study	7983	55-64	0.90		
				65-74	4.00		
				75-84	9.70		
				85+	17.40		
Copenhagen(47)	1997 to 2000	Population-based cohort study	764		Men	Women	
				50-59	1.80	0.80	
				60-69	2.00	1.00	
				70-79	6.30	3.60	
				80-89	13.90	4.30	
				Total	4.20	2.30	
Portugal(48)	1998	Cross-sectional observational study	5434	25-49	1.36		
				50-59	2.93		
				60-69	7.63		
				70-79	12.67		
				80+	16.14		
Copenhagen(49)	1993 to 1995	Cross-sectional primary care-based study	2158	40-49	0.50		
				50-59	1.50		
				60-69	4.80		
				70-79	9.30		
				80+	11.70		
Asturias, Spain(50)	1995 to 1999	Cross-sectional study	391	40-49	<1.00		
				50-59	2.00		
				60-69	5.00		
				70-79	13.00		
				80+	18.00		
Goteborg(22)	1970 to 1996	Population-based cohort study	7495		Men		
				55-64	0.60		
				65-74	2.80		
				75-79	6.20		
Rotterdam(51)	1990 to 1993	Population-based cohort study	5540		Men	Women	Total
				Prevalence of HF			
				55-64	0.70	0.60	0.70
				65-74	3.70	1.60	2.70
				75-84	14.40	12.10	13.00
				85-94	5.90	14.00	11.70
				Total	3.10	3.00	3.00
				Prevalence of LVSD FS≤25%			
				55-64	3.70	1.20	2.30
				65-74	7.60	3.10	5.30
				75-84	6.90	3.30	4.80
				85-94	10.00	10.50	10.30
				Total	5.50	2.20	3.70
Goteborg(52)	1963 to 1980	Population-based cohort study	973	Prevalence of manifest HF (men)			
				50		2.10	
				54		2.40	
				60		4.30	
				67		13.00	
U.S.							
Georgia(30)	2000 to 2005	Retrospective, hospitalised and outpatient-based cohort study	359947		Men	Women	
				2000			
				18-54	0.41	0.34	
				55-64	3.35	2.41	
				65-74	8.05	5.87	
				≥75	17.00	15.68	
				2001			
				18-54	0.47	0.41	
				55-64	3.53	2.67	
				65-74	8.03	6.07	
				≥75	15.62	15.78	
				2002			
				18-54	0.53	0.47	
				55-64	4.13	2.89	
				65-74	8.54	7.11	
				≥75	17.01	17.19	

				2003		
				18-54	0.57	0.51
				55-64	4.25	3.07
				65-74	9.68	7.29
				≥75	18.61	17.17
				2004		
				18-54	0.60	0.54
				55-64	4.42	3.22
				65-74	10.48	7.63
				≥75	18.37	17.74
				2005		
				18-54	0.60	0.52
				55-64	4.64	3.17
				65-74	10.14	7.68
				≥75	19.75	17.67
US (104)	2003-2006	National statistics	-		Men	Women
				20-39	0.30	0.20
				40-59	1.90	1.40
				60-79	9.10	4.90
				≥80	14.7	12.80
Heart Disease and Stroke Statistics 2007(31)	1999 to 2004	National statistic	5.2 million		Men	Women
				20-39	0.30	0.20
				40-59	2.00	1.50
				60-79	7.20	5.20
				80+	11.60	12.40
Cleveland(53)	1998 to 2000	Prospective, hospitalisation-based cohort study	481	Prevalence of asymptomatic LVEF≤45%		
				60-64	7.80	
				65-69	5.90	
				70-74	10.50	
				75+	7.70	
Rochester(54)	1997 to 2000	Population-based cohort study	2042	45-54	0.70	
				55-64	1.30	
				65-74	1.50	
				75+	8.40	
Rochester(54)	1997 to 2000	Population-based cohort study	2042		Men	Women	Total
				Prevalence of LVEF≤50%			
				45-54	5.10	1.00	3.00
				55-64	7.40	2.20	4.80
				65-74	10.60	3.80	7.10
				75+	22.80	6.60	12.90
				Prevalence of LVEF≤40%			
				45-54	1.70	0.00	0.80
				55-64	1.90	0.60	1.30
				65-74	4.70	0.80	2.70
				75+	7.90	2.20	4.40
National Health Interview Survey(55)	1999	Cross-sectional study	30801		Men	Women	Total
				18-39	0.04	0.10	0.10
				40-64	1.20	1.10	1.10
				65-74	4.50	2.90	3.60
				75+	5.70	5.30	5.30
Third National Health and Nutrition Examination Survey(56)	1988 to 1994	Population-based, cross-sectional surveys	5549		Men	Women	Total
				40-49	0.20	0.20	0.30
				50-59	3.90	2.00	2.90
				60-69	6.30	5.60	5.80
				70-79	10.80	5.90	8.10
				≥80	6.10	8.70	7.80
Framingham(39)	1987 to 1990 (original cohort) 1991 to 1995 (offspring cohort)	Population-based cohort study	4257		Men	Women
				Prevalence of asymptomatic LVEF≤50%		
				40-59	2.10	0.50
				60-69	7.20	0.80
				70-79	11.30	1.00
				80+	14.30	1.90
				All	6.00	0.80
Framingham(28)	40 years follow up	Population-based cohort study			Men	Women
				50-59	0.80	0.80
				80-89	6.60	7.90
Framingham(57	34 years	Population-based cohort		50-59	0.80	

)	follow up	study		60-69	2.30		
				70-79	4.90		
				80-89	9.10		
Rochester(58)	1986	Cross-sectional study	2122		Men	Women	Total
				35-54	0.00	0.20	0.10
				55-64	0.50	0.50	0.50
				65-74	2.30	0.00	1.20
				75+	6.90	8.00	7.60
				35+	1.76	2.09	1.93
Rochester(29)	1981 to 1982	Cross-sectional study	-		Men		Women
				45-49	0.10		0.10
				50-54	0.10		0.20
				55-59	0.70		0.30
				60-64	1.20		0.70
				65-69	2.60		1.10
				70-74	2.80		2.70
				0-74	0.33		0.21
National Health and Nutrition Examination Survey I(59)	1971 to 1975	Population-based cohort study	14407		Men	Women	Total
				Self reported HF			
				25-54	0.40	0.30	0.40
				55-64	2.20	2.00	2.10
				65-74	3.70	3.20	3.40
				25-74	1.10	1.00	1.10
				HF diagnosed using clinical score			
				25-54	0.80	1.30	1.10
				55-64	4.50	3.00	3.70
				65-74	4.80	4.30	4.50
				25-74	1.90	2.00	2.00
Others							
Canberra, Australia(60)	2002 to 2003	Cross-sectional survey	1275		Men	Women	Total
				60-64	3.60	2.60	3.10
				65-69	7.30	2.00	4.80
				70-74	5.20	4.80	5.00
				75-79	17.80	7.80	12.40
				80-86	15.70	10.40	13.60
				Total	8.20	4.40	6.30
Arab(61)	1992 to 1994	Prospective, hospitalisation-based cohort study	225000	<45	0.11		
				45-64	1.57		
				≥65	2.52		
				Overall	0.52		
Taiwan(62)	1991 to 1993		2660		Men	Women	Total
				Prevalence of LVEF<55%			
				35-44	12.10	8.00	9.60
				45-54	11.10	9.20	10.00
				55-64	12.70	11.80	12.30
				65-74	11.60	9.80	10.70
				>75	14.30	4.30	9.30
				All	12.00	9.30	10.50

1.3.5 Mortality in young adults with HF

Table 1.4 summarises the in-hospital, thirty-day, one-, two-, three-year, and five-year mortality rates in young adults with HF. I have only included studies reporting mortality rate from year 2000 onwards.

The in-hospital mortality in young adults with HF is low from 1.2% to 3.5%.(63-65) Similarly, the 30 days mortality in young adults is also low 2.6% to 3.7%.(12;66) One Scottish study included patients from 1986 to 2003 reported higher 30 days mortality of 9.6% compared to the previous two studies which included patients from 2002-2005 and 2009, respectively.(67) Younger adults have lower 1 year mortality and increases with age.(12;17;67) In Scotland 5 year survival rates were 39.5% and 56.4% in those aged <55 and 55-64 years, respectively.(67) Contemporary study reporting long-term mortality in young adults with HF is lacking.

In Sweden the mortality rate has improved between 1987 and 2003. Younger patients aged 35-64 years had the best improvement in 3 year mortality rate after first hospitalisation with a diagnosis of HF compared to patients aged 65-84 years (Period 1999-2001 vs. 1987-1989: Men aged 35-64 years 17% vs. 39%; Women aged 35-64 years 19% vs. 31%; Men aged 65-84 years 41% vs. 57%; Women aged 65-84 years 36% vs. 50%; all $p<0.0001$).(68) An updated analysis of this database stratified the younger patients (<55 years) into 18-34, 35-44, and 45-54 years demonstrated marked improvement in 1 year mortality in all age groups from 1987-1991 to 1997-2001 with no further improvement after 2001 compared to those aged 55-84 years which mortality continues to improve.(17)

Table 1.4. Mortality of HF in young adults with HF

Study	Year of study	Number of patients	Mortality	
In-hospital				
Qatar(64)	1991-2010	7066	99-02	
			<50	9.2%
			51-70	10..4%
			>70	13.9%
			03-06	
			<50	8.4%
			51-70	6.5%
			>70	9.4%
			07-10	
			<50	3.5%
			51-70	4.2%
			>70	7.0%
US(63)	2001-2009	1 686 089	2001	
			18-44	1.7%
			45-54	1.6%
			55-64	2.7%
			65-74	3.6%
			≥75	6%
			2002	
			18-44	1.6%
			45-54	1.7%
			55-64	2.4%
			65-74	3.5%
			≥75	5.8%
			2003	
			18-44	1.6%
			45-54	1.7%
			55-64	2.3%
			65-74	3.3%
			≥75	5.6%
			2004	
			18-44	1.7%
			45-54	1.7%
			55-64	2.4%
			65-74	3.2%
			≥75	5.4%
			2005	
			18-44	1.2%
			45-54	1.6%
			55-64	1.9%
			65-74	2.9%
			≥75	5.2%
			2006	
			18-44	1.4%
			45-54	1.3%
			55-64	1.9%
			65-74	2.8%
			≥75	4.9%
			2007	
			18-44	1.4%
			45-54	1.3%
			55-64	1.7%
			65-74	2.5%
			≥75	4.6%
			2008	
			18-44	1.4%
			45-54	1.3%
			55-64	1.6%
			65-74	2.5%
			≥75	4.5%
			2009	

			18-44	1.5%	
			45-54	1.3%	
			55-64	1.7%	
			65-74	2.5%	
			≥75	4.5%	
France(66)	2009	69968	<55	2.0%	
			55-69	2.9%	
			70-79	4.3%	
			80-89	7.6%	
			≥90	12.8%	
US(65)	2007-2008	430665		Men	Women
			20-24	2.7%	2.5%
			25-29	1.7%	1.6%
			30-34	1.5%	1.3%
			35-39	0.9%	0.9%
			40-44	1.0%	1.2%
			45-49	1.3%	0.9%
			50-54	1.3%	1.0%
			55-59	1.3%	1.3%
			60-64	2.0%	1.5%
			65-69	2.2%	1.9%
			70-74	2.9%	2.4%
			75-79	3.2%	2.9%
			80-84	4.3%	3.8%
			85-89	5.2%	4.4%
			90-94	6.9%	6.0%
			≥95	8.7%	7.1%
GWTG-HF(69)	2005 to 2007	57937	≤65	1.6%	
			66-77	3.1%	
			76-85	3.8%	
			≥85	5.3%	
NHS HF survey(70)	2005 to 2006	9387	<55	<3%	
			>85	23%	
Taiwan(10)	2005	2692	20-64	2.7%	
			≥65	4.2%	
			All	3.9%	
Worcester(71)	2000	2604	<55	1.7%	
			55-64	2.6%	
			65-74	2.5%	
			75-84	7.0%	
			≥85	6.1%	
30 days mortality					
France(66)	2009	69968	<55	3.7%	
			55-69	5.1%	
			70-79	7.3%	
			80-89	12.7%	
			≥90	21.6%	
Western Australia(12)	1990 to 2005	27105	1990-1993		
			<65	6.5%	
			65-74	10.6%	
			≥75	13.7%	
			1994-1997		
			<65	4.3%	
			65-74	8.1%	
			≥75	11.2%	
			1998-2001		
			<65	3.8%	
			65-74	6.7%	
			≥75	11.4%	
			2002-2005		
			<65	2.6%	
			65-74	6.3%	
			≥75	10.9%	

Scotland(67)	1986 to 2003	116556	<55	9.6%
			55-64	12.4%
			65-74	16.8%
			75-84	21.4%
			≥85	25.6%
1 year mortality				
Sweden(17)	1987 to 2006	443995	1987-1991	
			18-34	28.3%
			35-44	25.1%
			45-54	25.4%
			55-84	39.1%
			1992-1996	
			18-34	19.9%
			35-44	18.1%
			45-54	17.2%
			55-84	30.4%
			1997-2001	
			18-34	12.3%
			35-44	12.6%
			45-54	13.7%
			55-84	27.8%
			2002-2006	
			18-34	12.2%
			35-44	10.6%
			45-54	12.2%
			55-84	26.6%
Western Australia(12)	1990 to 2005	27105	Overall	
			<65	13.4%
			65-74	22.4%
			≥75	33.0%
			1990-1993	
			<65	18%
			65-74	25.8%
			≥75	36.4%%
			1994-1997	
			<65	15.3%
			65-74	22.8%
			≥75	33.9%
			1998-2001	
			<65	12.0%
			65-74	21.3%
			≥75	31.7%
			2002-2005	
			<65	8.9%
			65-74	18.2%
			≥75	29.8%
Japan(72)	2004 to 2005	2685	Managed in cardiology clinic	
			15-39	11.1%
			40-49	1.9%
			50-59	3.0%
			60-69	3.4%
			70-79	6.6%
			80-89	10.5%
			90-101	13.2%
			Managed by GP	
			15-39	0%
			40-49	0.0%
			50-59	0.0%
			60-69	1.5%
			70-79	3.8%
			80-89	8.3%
			90-101	18.5%
Scotland(67)	1986 to 2003	116556	<55	22.0%
			55-64	30.4%
			65-74	40.0%
			75-84	48.6%
			>84	57.2%

3 year mortality						
Sweden(68)	1987 to 2003	179753			Men	Women
			Aged 35-64 years			
			87-89		39.0%	31.0%
			90-92		34.0%	27.0%
			93-95		24.0%	22.0%
			97-99		22.0%	21.0%
			99-01		17.0%	19.0%
			Aged 65-84 years			
			87-89		57.0%	50.0%
			90-92		52.0%	46.0%
			93-95		46.0%	39.0%
			97-99		43.0%	38.0%
			99-01		41.0%	36.0%
5 year mortality						
Scotland(67)	1986 to 2003	116556	<55	39.4%		
			55-64	56.4%		
			65-74	69.4%		
			75-84	80.7%		
			>84	89.3%		

1.3.6 Cause of death in young adults with HF

The only study I found reporting cause of death in young adults is the Amiodarone Trialists' meta-analysis.(73) The study included 6252 patients stratified into ≤50, 51-60, 61 to 70, 71 to 80, and >80 years demonstrated that younger patients were more likely to die suddenly compared to their older counterparts (≈50% of all death in patient ≤50 years was sudden death vs. 26% of all death in patient >80 years).(73)

1.3.7 HF Hospitalisations in young adults with HF

Table 1.5 summarises HF hospitalisation rate in young adults with HF. The hospitalisation rate in young adults with HF is lower compared to older patients with men displaying higher hospitalisation rates. However, very young adults with HF have not experienced the same decline in HF hospitalisation as their older counterpart.

In the US National Inpatient Sample dataset, young adults aged 20-24 years have the lowest HF hospitalisation rate (12.5 per 100000) and increases with age consistent with other studies.(3;12;65) An updated analysis from the same dataset examined trend of HF hospitalisation from 2001 to 2009 reported no significant decline in HF hospitalisation in patients aged 18-44 and 45-54 years similar other studies which suggest the largest decline in HF hospitalisations are in the older patients.(12;63;74)

Table 1.5. HF hospitalisation rate in young adults with HF

Study	Year of study	Number of patients	Hospitalisation (per 100,000)					
US(63)	2001-2009	1 686 089	Primary diagnosis					
				18-44	45-54	55-64	66-74	75+
			2001	44.00	247.00	704.00	1709.00	4272.00
			2002	45.00	254.00	653.00	1608.00	3894.00
			2003	45.00	245.00	649.00	1552.00	3827.00
			2004	48.00	259.00	640.00	1541.00	3868.00
			2005	48.00	248.00	593.00	1487.00	3861.00
			2006	49.00	257.00	563.00	1372.00	3624.00
			2007	47.00	241.00	526.00	1266.00	3373.00
			2008	41.00	207.00	462.00	1089.00	3102.00
			2009	38.00	207.00	447.00	1070.00	3064.00
			Δ (%)	-12.80	-16.20	-36.50	-37.40	-28.30
			P	0.570	0.036	<0.001	<0.001	<0.001
US(74)	2001-2009			18-49	50-64	65-74	75-84	85+
			Primary diagnosis					
			2001-2003	59.00	456.00	1415.00	2899.00	5235.00
			2004–2006	65.00	431.00	1293.00	2681.00	5002.00
			2007-2009	61.00	384.00	1095.00	2373.00	4521.00
			Secondary diagnosis					
			2001-2003	108.00	983.00	3462.00	7601.00	14784.00
			2004–2006	131.00	1071.00	3641.00	7906.00	14991.00
			2007-2009	134.00	1045.00	3376.00	7303.00	13499.00
US(65)	2007-2008	430665	Primary diagnosis					
				Men	Women			
			20-24	15.00	10.00			
			25-29	24.00	17.00			
			30-34	43.00	28.00			
			35-39	74.00	40.00			
			40-44	124.00	74.00			
			45-49	193.00	116.00			
			50-54	302.00	200.00			
			55-59	431.00	301.00			
			60-64	667.00	476.00			
			65-69	1076.00	773.00			
			70-74	1582.00	1220.00			
			75-79	2323.00	1782.00			
			80-84	3434.00	2701.00			
			≥85	5340.00	4407.00			
Tennessee, US(75)	2006-2008	20222 (2006); 16889 (2008)	Primary diagnosis					
				Men	Women			
			2006					
			20-34	22.00	14.00			
			35-44	95.00	64.00			
			45-54	243.00	190.00			
			55-64	561.00	424.00			
			65-74	1216.00	1038.00			
			75-84	2474.00	2066.00			
			≥80	4310.00	3769.00			

			2008		
			20-34	19.00	11.00
			35-44	85.00	52.00
			45-54	207.00	146.00
			55-64	454.00	333.00
			65-74	1049.00	819.00
			75-84	2088.00	1651.00
			≥80	3741.00	3246.00
US(76)	1997 and 2006	15614 (1997) 20459 (2006)	Primary diagnosis		
				Men	Women
			1997		
			25-34	12.00	10.00
			35-44	51.00	52.00
			45-54	169.00	149.00
			55-64	512.00	409.00
			65-74	1169.00	959.00
			75-84	2321.00	1950.00
			≥85	3867.00	3667.00
			2006		
			25-34	22.00	14.00
			35-44	97.00	64.00
			45-54	248.00	190.00
			55-64	569.00	424.00
			65-74	1234.00	1046.00
			75-84	2498.00	2086.00
			≥85	4337.00	3812.00
Switzerland(77)	2005	8120		Men	Women
			25-34	2.20	1.80
			35-44	6.90	2.90
			45-54	25.70	8.20
			55-64	80.80	31.50
			65-74	269.70	132.70
			75-84	836.40	491.30
			≥85	1821.70	1228.40
Western Australia(12)	1990 to 2005	19342	Primary diagnosis		
				Men	Women
			Aged <65 years		
			90-93	71.78	37.07
			94-97	65.37	34.68
			98-01	58.38	37.49
			02-05	59.23	33.68
			Aged 65-74 years		
			90-93	852.36	595.39
			94-97	908.88	571.28
			98-01	751.90	504.15
			02-05	626.00	352.96
			Aged ≥75 years		
			90-93	2435.62	2136.97
			94-97	2696.71	2136.07
			98-01	2645.28	2110.67
			02-05	2122.86	1724.85
			Overall		
			<65	63.03	35.78
			65-74	757.29	488.36
			≥75	2410.40	1974.77
U.S. National Hospital Discharge Survey(3)	1979 to 2004		HF as principal diagnosis		
				Men	Women
			Aged <65 years		
			1979	50.90	39.30
			2004	134.00	98.20
			RPC	+163.2%	+149.7%
			Aged 65-74 years		
			1979	865.60	667.90
			2004	1469.70	1161.10
			RPC	+69.8%	+67.1%
			Aged ≥75 years		
			1979	2288.80	1976.70
			2004	3788.90	3402.40

			RPC	+65.5%	+72.1%	
Spain(78)	1996	1069	Principal or any diagnosis and fulfilled criteria			
				Men	Women	Total
			15-39	4.60	1.50	3.10
			40-64	120.00	84.00	100.00
			65-79	680.00	580.00	620.00
			≥80	1890.00	2080.00	2020.00
			All	170.00	220.00	200.00
France(79)	1992 to 1996	138543	Primary diagnosis			
				White		
			15-44	90.00		
			45-64	670.00		
			65-74	1980.00		
			75-84	4100.00		
			≥85	6530.00		
Minnesota(80)	1995	5503	All discharges			
				Men	Women	
			35-44	36.00	20.00	
			45-54	144.00	103.00	
			55-64	560.00	403.00	
			65-74	1691.00	1181.00	
			75-84	4055.00	2703.00	
			Overall	549.00	486.00	
Spain(81)	1980 to 1993	42961 (1980); 73442 (1993)	Primary diagnosis			
				Men	Women	Total
			Aged 45-64 years			
			1980	275.15	168.70	219.98
			1993	266.36	162.61	212.82
			Change	-3.30%	-3.61	-3.25%
			Aged >65 years			
			1980	732.06	508.29	599.49
			1993	1014.59	932.65	954.85
			Change	38.9%	83.49%	59.28%

1.4 Aetiology of HF in young adults with HF

The majority of HF in very young adults is caused by conditions other than coronary heart disease (Table 1.6). The younger the patient the more likely they are to have a non-ischaemic aetiology. Reporting of aetiology will not represent exhaustive investigation. Few have investigated sub-groups of dilated cardiomyopathy. How many of these patients labelled with dilated cardiomyopathy have adult congenital heart disease or other causes of HF beyond the most common causes is unknown. In the CARE-HF trial, among all the patients with investigators reported dilated cardiomyopathy, only 40% of them were truly idiopathic after excluding patients without any previous coronary angiography, patients with coronary artery disease or diabetes or hypertension or combination of these.(82)

Table 1.6. Aetiology of HF in young adults with HF

Study	Aetiology (%)											
Clinical trials												
Pooled analysis of 5 randomised controlled trials(83) N=11642		Male Ischaemic		Nonischaemic		Female Ischaemic		Nonischaemic				
	N	5021		3770		1134		1717				
	<65	43		65		38		60				
	65-74	41		25		40		28				
	75+	16		9		22		12				
HF ACTION study(84) N=2331		<60		60-69		≥70						
	N	1214		640		477						
	Ischaemic	37.6		61.9		72.3						
	p<0.001											
CARE HF(82) N=813	Age	<60		60-70		>70						
	N	219		315		277						
	Ischaemic	25		38		49						
	Hypertension	6		10		10						
	DCM	58		45		36						
	Alcohol related	5		2		0						
	Valve	3		2		2						
	Other	3		2		3						
MERIT-HF(85) N=3991		<65				≥65						
		Placebo		Metoprolol CR/XL		Placebo		Metoprolol CR/XL				
	N	1009		1000		992		990				
	Ischaemic	56		55		75		75				
	p<0.0001											
LVAD(86) N=222		≤44		45-53		53-59		≥60				
	N	55		55		56		56				
	Ischaemic	15		60		65		54				
	p<0.01											
DIG Study(87) N= 7788		<50		50-59		60-69		70-79		≥80		
	N	841		1545		2885		2092		425		
	Ischemic	50		67.5		72.5		73		68.5		
	Non-ischemic	50		32.5		27.5		27		31.5		
Arab(61) N=1164		13-24		25-34		35-44		45-54		55-64		≥65
	N	18		43		120		194		435		353
	Ischaemic	0		9		43		41		56		64
	Hypertensive	0		16		18		26		30		23
	Idiopathic	28		23		17		12		6		3
	Valvular	33		37		14		4		0		0
PRIME-II study(88) N=311				38-62		63-69		70-73		74-80		
	N			76		77		67		91		
	Coronary artery disease			68		83		72		78		
	DCM			25		12		18		14		
	Hypertension			3		4		3		8		
	Other			4		1		7		0		
AREA IN-CHF study(89) N=467				<64				≥64				
	N			232				235				
	Ischaemic			51				52				
	Idiopathic			33				27				
	Hypertensive			7				13				
	Valvular heart disease			3				5				
	Other			4				1				
	p not significant											
North American centers(90) N=546				<65				≥65				
	N			328				218				
	Ischaemic			38				73				
	Hypertensive			9				6				
	Idiopathic			40				17				
	Others			13				4				
	p<0.001											
Val-HeFT(91) N= 5010				<65				≥65				
	N			2660				2350				
	Ischaemic			49.3				66.1				

	p<0.001								
BEST study(92)		<65		≥65					
N= 270	N	1616		1092					
	Ischaemic	49		73					
	p<0.001								
Registry/ Prospective cohort									
Get With the Guidelines-HF(69)		≤65		66-77		76-85		>85	
N=57937	N	16245		12488		18398		10806	
	Ischaemic HF	31.9		44.9		42.5		32.5	
	p<0.0001								
IMPROVE HF(93)		≤64		65-76		>76			
N= 15381	N	5307		5176		4791			
	Ischaemic	53		71		73			
	Non-ischaemic	25		12		10			
	Valvular	2		2		2			
	Other	13		8		7			
	p<0.001								
IMPROVEMENT of HF survey(94)		<65	65-74		75-84		≥85		All
N=8256	N	2574	2549		2243		890		8256
	Coronary heart disease	46	47		43		34		44*
	Hypertension	23	25		26		22		24*
	Valvular	8	8		9		9		9
	Idiopathic	6	3		2		2		4*
	Other	17	17		20		33		19*
	*statistically significant, p<0.001								
The Carvedilol Heart Failure Registry(95)		<55		55-64		65-75		>75	
N=4280	N	806		922		1363		1188	
	Ischaemic	34		55		62		63	
	Hypertensive	18		16		14		16	
	Idiopathic	31		19		14		11	
	Other	16		9		10		10	
	p<0.001								
Italian Network on Congestive Heart Failure Registry(96)		≤65		66-75		≥75			
		AF	No AF	AF	No AF	AF	No AF		
N= 8178	N	683	3578	638	2013	412	854		
	Ischaemic	18	37	28	52	33	49		
	Valvular	22	6	27	8	20	12		
	Hypertensive	12	9	17	14	23	20		
	Idiopathic	39	42	23	23	17	15		
	Other	9	6	5	3	8	4		

AF=atrial fibrillation; AREA IN-CHF= AntiREmodelling Effect of Aldosterone Receptors Blockade with Canrenone IN Mild Chronic Heart Failure) study; BEST=Beta-Blocker Evaluation in Survival Trial; CARE-HF= the Cardiac Resynchronization-Heart Failure study; DIG=Digitalist Investigation Group; IMPROVE-HF=The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; LVAD=left ventricular assist device; MERIT-HF=The Metoprolol CR/XL Randomised Intervention Trial in Chronic Heart Failure; PRIME-II=Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy.

1.5 Co-morbidities in young adults with HF

Table 1.7 illustrates the co-morbidities in young adults with HF. Young adults (<65 years) have a lower prevalence of hypertension, prior myocardial infarction, atrial fibrillation, hyperlipidaemia, chronic kidney disease, stroke or transient ischaemic attack, peripheral artery disease and malignancy.(10;69;93-95;97-99). The prevalence of diabetes in young adults with heart failure are conflicting with some suggesting it is higher and some lower comparing to older patients.(10;33;69;87;93;94;97-99).

Comparing to older patients, younger adults were more likely to have depression (<65 years: 10.4% vs. ≥65 years: 8%),(93) and misuse alcohol (≤65 years: 2.6%, 66-77 years: 0.9%, 76-85 years: 0.4% and >85 years: 0.1%; p<0.0001).(69) Cigarette smoking is also more common in young adults <65 years.(69;98)

All these studies have defined young as <50-65 years. None has further stratified them into smaller age group. The trends of comorbidities in young adults are yet to be investigated.

Table 1.7. Co-morbidities in young adults with HF

Study	Co-morbidities (%)	Age			
SHIFT trial(100)		<53	53- <60	60- <69	≥69
N=6505	N	1522	1521	1750	1712
	Ischaemic HF	48	69	73	79
	AF/ flutter	5	6	8	12
	MI	42	59	60	63
	Hypertension	52	68	70	75
	Stroke	4	7	10	10
	Diabetes	21	35	34	32
	Renal failure	3	4	6	12
	All p<0.0001				
IMPROVE HF(93)		≤64	65-76	>76	
N= 15381	N	5307	5176	4791	
	Atrial fibrillation	20	32	41	
	Diabetes	35	38	29	
	Hypertension	58	64	64	
	Prior MI	34	43	42	
	COPD	13	20	17	
	CABG	22	37	35	
	PVD	8	14	13	
	Depression	10	8	8	
	All p<0.001				
GWTG-HF(69)		≤65	66-77	76-85	>85
N=57937	N	16245	12488	18398	10806
	HF	24	24	23	23
	CAD/IHD	32	45	44	36*
	Hypertension	59	60	58	56*
	AF	13	24	31	32*
	Hyperlipidaemia	28	36	32	21*
	CRI	14	18	17	14*
	Anaemia	10	13	15	16*
	Pulmonary disease	23	27	24	18*
	DM(no insulin)	19	19	12	6*
	DM (insulin)	19	24	20	13*
	Alcohol abuse	3	1	0	0*
	Tobacco	33	16	7	2*
	*p<0.0001				
HF ACTION		<60	60-69	≥70	
study(84)	N	1214	640	477	
N=2331	Diabetes mellitus	29	38	32*	
	COPD	7	13	15*	
	PAD	4	9	12*	
	*p<0.001				
InSync/InSync ICD		<65	65-74	≥75	
Italian Registry(97)	N	571	740	476	
N= 1787	COPD	5	7	6	
	Diabetes Mellitus	8	9	6	
	Hypertension	13	18	20*	
	Renal failure	3	8	4*	
	≥3 co-morbidities	4	9	7*	
	CAD	39	50	50*	
	Permanent AF	11	18	21*	
	*statistically significant				
Taiwan(10)		20-64	≥65	All	
N=2692	N	567	2125	2692	
	Diabetes mellitus	36	26	28*	

	Hypertension	41			38			39			
	COPD	9			22			19*			
	Stroke	6			10			9*			
	Nephropathy	18			11			13*			
	Cancer	4			5			5			
	Infection	23			32			30*			
	Digestive disease	19			23			22			
	IHD	30			32			32			
	PAD	4			2			1*			
	*statistically significant										
Kent, Surrey and Sussex Primary Care Research Network(33) N= 2129		45-54		55-64		65-74		75-84		85+	
		M	W	M	W	M	W	M	W	M	W
	Atrial fibrillation	15	0	31	15	33	23	33	27	26	28
	Diabetes	20	18	28	21	22	22	15	15	10	9
	Hypertension	35	36	42	40	42	48	41	50	35	42
	Coronary artery disease	50	27	55	29	57	43	45	38	40	35
MERIT-HF(85) N=3991		<65				≥65			
		Placebo		Metoprolol CR/XL		Placebo		Metoprolol CR/XL	
	N	1009		1000		992		990	
	Previous MI	42		40		55		56*	
	Hypertension	42		44		46		44	
	DM	23		25		26		25	
	AF	13		12		20		19*	
	*p<0.0001								
DIAMOND study and ECHOS(101) N= 8507		<65		65-74		75-84		≥85		All	
	N	1865		2769		3048		825		8507	
	Cardiovascular comorbidities										
	IHD	48		56		53		42		52	
	Hypertension	24		27		26		20		25	
	Diabetes	16		17		16		12		16	
	Stroke/TIA	6		11		11		11		10*	
	Previous MI	35		38		34		22		34*	
	Atrial fibrillation	16		24		25		20		22*	
	PAD	6		8		6		4		6	
	Associated comorbidities										
	COPD	22		26		23		14		23*	
	Anaemia	2		3		4		5		3*	
	Depression	2		2		1		2		2	
	Severe dementia	0		0		0		1		0*	
	Renal insufficiency	2		6		17		35		11*	
	Myxoedema	1		2		3		3		2*	
	Hyperthyroidism	1		1		2		2		2*	
	Cancer history	2		4		5		6		4*	
	Arthritis urica	5		6		5		5		5	
	Rheumatic arthritis	1		2		2		2		2*	
	Polymyalgia rheumatic	0		1		2		2		1*	
	Colitis ulcerosa	0		0		0		0		0	
	Gastro intestinal ulcer	4		6		5		5		5	
	Total of ≥3	20		32		33		26		29*	
	Cardiovascular ≥2	32		43		41		30		39	
	*statistically significant										
IMPROVEMENT of HF survey(94) N=8256		<65		65-74		75-84		≥85		All	
	N	2574		2549		2243		890		8256	
	CAD	46		43		37		23		40*	
	Cerebrovascular disease	9		16		19		21		16*	

	PVD	16	21	21	18	19*
	Hypertension	61	67	64	62	64
	Diabetes	19	23	19	13	20*
	Pulmonary disease	27	35	32	28	31
	Renal dysfunction	10	19	25	32	19*
	AF	16	25	31	36	25*
	*statistically significant					

DIAMOND study(98) N= 5419		<61	61-70	71-80	>80
	N	718	1481	2203	1089
	IHD	51	60	59	51*
	Previous MI	35	42	39	28*
	Hypertension	22	26	26	20*
	Valvular disease	3	4	4	3
	COPD	20	24	25	17*
	Diabetes	13	19	17	15*
	Atrial fibrillation	16	23	27	27*
	Current Smoking	52	41	31	19*
	*statistically significant				

DIG study(87) N= 7788		<50		50-59		60-69		70-79		≥80	
		D	P	D	P	D	P	D	P	D	P
	N	437	404	748	797	1465	1420	1013	1079	226	199
	MI	45	50	64	63	67	67	66	64	56	59
	HTN	43	44	43	45	48	47	50	51	48	49
	DM	19	22	29	30	32	31	28	30	17	19
	D=digoxin; P=placebo										

The Carvedilol Heart Failure Registry(95) N=4280		<55	55-64	65-75	>75
	N	806	922	1363	1188
	Prior MI	28	43	47	41
	Hypertension	51	58	60	61
	Diabetes	30	39	34	25
	Angina	21	26	30	29
	All p<0.001				

CHARM study(99) N=7599		<50	50-59	60-69	70-79	>80
	N	605	1474	2351	2474	695
	Diabetes	22.1	29.8	31.5	28.6	20.4*
	Hypertension	43.3	51.9	55.8	58.0	59.1*
	Atrial fibrillation	12.4	19.2	24.6	34.2	43.3*
	*p<0.001					

North American centers(90) N=546		<65	≥65
	N	328	218
	Prior MI	33	51*
	Prior PCI	14	13
	Prior CABG	18	42*
	Peripheral arterial disease	4	11*
	Stroke	8	10
	Hypertension	52	63*
	Hyperlipidaemia	43	56*
	Ventricular arrhythmia	21	22
	Atrial fibrillation/ flutter	25	37*
	Pacemaker	9	25*
	Implantable defibrillator	14	15
	Diabetes	31	37
	COPD or Asthma	15	24*
	Depression requiring treatment	13	11
	Arthritis	7	13*
	Malignancy	4	11*
	Renal failure	4	9*
	Current Alcohol use	52	50

	Alcohol abuse history	22		11*	
	Smoking (any)	62		57*	
	Current/recent Tobacco use	28		13*	
	Illicit drug use	9		2*	
	*Statistically significant				
AREA IN-CHF study(89) N=467		<64		≥64	
	N	232		235	
	Previous admission for HF	47		47	
	Previous MI	48		51	
	Previous revascularisation	36		35	
	Stroke	1		3	
	Chronic AF	5		11	
	Hypertension	42		49	
	Diabetes	14		27	
	Current smoker	18		10	
	Ex-smoker	44		46	
V-HeFT I and II(102) N= 1446		≤55	56-60	51-65	>65
	V-HeFT I				
	N	185	182	170	105
	Coronary artery disease	35	47	52	41
	Hypertension	30	45	46	37
	V-HeFT II				
	N	175	173	231	225
	Coronary artery disease	41	57	55	58
	Hypertension	40	57	55	58

AF=atrial fibrillation; CABG=coronary artery bypass grafting; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; CRI=chronic renal impairment; DM=diabetes mellitus; HF=heart failure; HTN=hypertension; IHD=ischaemic heart disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; PAD=peripheral artery disease; PVD=peripheral vascular disease; TIA=transient ischaemic attack.

1.6 Symptoms and signs of HF in young adults with HF

1.6.1 Symptoms

There are limited data on symptoms of HF by age categories (Table 1.8). Younger adults have better NYHA functional class. The DIG trial dichotomised age at 65 years of age reported no difference in proportions in dyspnoea at rest and on exertion.(103) No other trials or studies have examined the differences in symptoms of HF in detail in young adults with HF.

1.6.2 Signs

From the limited data that has been published, younger adults with HF have different signs of HF (Table 1.8). Younger patients are less likely to have pulmonary rales,(82;85;103) and less likely to have peripheral oedema.(82;85;103) Further studies are needed to examine the differences in signs of HF in young adults with HF.

Table 1.8. Symptoms, signs, and NYHA functional classes in young adults with HF

Study	Symptoms and signs & NYHA functional classes (%)									
Clinical trials										
SHIFT(100)		<53		53- <60		60- <69		≥69		
N=6505	NYHA	n=1522		n=1521		n=1750		n=1712		
	II	55		48		51		41		
	III	43		51		47		56		
	IV	2		1		2		3		
	All p<0.0001									
CARE HF(82)		<60		60-70		>71				
N=813	N	219		315		277				
	Pulmonary rales	5		12		17				
	Peripheral oedema	13		19		22				
	3rd heart sound	16		20		22				
	JVP elevated	14		18		21				
HF ACTION		<60		60-69		≥70				
study(84)	N	1214		640		477				
N=2331	NYHA									
	II	66.6		61.4		57.9				
	III	32.9		37.7		40.0				
	IV	0.6		0.9		2.1				
	p<0.001									
CHARM study(99)		<50	50-59	60-69	70-79	>80				
N=7599	N	605	1474	2351	2474	695				
	NYHA class									
	II	49	49	45	43	37				
	III	49	49	52	54	58				
	IV	2	2	3	3	5				
	p<0.001									
MERIT-HF(85)		<65			≥65					
N=3991		Placebo		Metoprolol CR/XL	Placebo		Metoprolol CR/XL			
	N	1009		1000	992		990			
	Peripheral oedema	14		16	15		15*			
	Jugular venous distension	14		14	13		13*			
	Pulmonary rales	10		10	12		12*			
	Third heart sound	22		24	24		23*			
	*not statistically significant									
	NYHA									
	II	46		45	37		36			
	III	51		52	59		60			
	IV	3.3		3.0	4.3		3.9			
	P<0.0001									
DIG study(87)		<50		50-59		60-69		70-79		≥80	
N= 7788		D	P	D	P	D	P	D	P	D	P
	N	437	404	748	797	1465	1420	1013	1079	226	199
	NYHA										
	I-II	75	75	72	72	69	69	65	66	57	55
	III-IV	25	25	28	28	31	31	35	34	43	45
Val-HeFT(91)		<65			≥65						
N= 5010	N	2660			2350						
	NYHA class III & IV	34			43						
	NYHA IV	2			2						
	p<0.001										
BEST(92)		<65			≥65						
N= 2708		Bucindolol		Placebo	Bucindolol		Placebo				
	N	821		795	533		559				
	NYHA III	93		93	89		89				
	NYHA IV	7		7	11		11				
	p=0.015										
DIG trial (103)		<65		≥65	p						
N=7788	N	3752		4036							
	Symptoms and signs of HF										
	Dyspnoea at rest	22		22	0.565						

	Dyspnoea on exertion	74	77	0.001					
	Jugular venous distension	12	14	0.031					
	Third heart sound	25	23	0.104					
	Pulmonary rales	13	20	<0.0001					
	Lower extremity oedema	20	22	0.010					
	NYHA functional class								
	I	16	13	<0.0001					
	II	56	53						
	III	27	32						
	IV	2	2*						
North American centers(90) N=546		<65		≥65					
	N	328		218					
	NYHA								
	I	13		8*					
	II	45		37*					
	III	38		50*					
	IV	5		6*					
	*statistically significant								
PRIME-II study(88) N=311		38-62	63-69	70-73	74-80				
	N	76	77	67	91				
	NYHA								
	III	78	68	72	63				
	III/IV	21	29	28	33				
	IV	1	3	0	4				
Registry									
The Carvedilol Heart Failure Registry(95) N=4280		<55	55-64	65-75	>75				
	N	806	922	1363	1188				
	NYHA III/IV	34	36	38	42				
	p<0.001								
IMPROVEMENT of HF survey(94) N=8256		<65	65-74	75-84	≥85	All			
	N	2574	2549	2243	890	8256			
	NYHA class								
	II	52	46	41	39	46			
	III	38	41	42	44	41			
	IV	11	13	17	17	14			
	p<0.001								
IMPROVE HF(93) N= 15381		≤64	65-76	>76					
	N	5307	5176	4791					
	NYHA class								
	I	21	21	18					
	II	28	25	26					
	III	18	17	18					
	IV	2	3	3					
	p=0.022								
Italian Network on Congestive Heart Failure Registry(96) N=8178		≤65		66-75		≥75			
		AF	No AF	AF	No AF	AF	No AF		
	N	683	3578	638	2013	412	854		
	Third heart sound	21	28	18	21	18	17		
	NYHA class III-IV	37	26	43	29	41	35		

D=Digoxin; NYHA=New York Heart Association functional class; P= placebo;

1.7 Investigations in young adults with heart failure

1.7.1 Electrocardiogram (ECG)

Younger adults with HF are more likely to be in sinus rhythm and less likely to be in atrial fibrillation or flutter.(88)

1.7.2 Chest Radiography

The Digitalis Investigation Group (DIG) and the Italian Network on Congestive Heart Failure, both reported lower proportions of cardiomegaly and pulmonary congestion in young adults aged <65 years compared to older patients.(87;96;103)

1.7.3 Echocardiogram

Younger adults (<50-65 years) have the lowest left ventricular ejection fraction and increases with age (Table 1.9). Mean left ventricular cavity size is greater in younger adults; left ventricular end diastolic diameter was 52mm in younger patients <61 years in comparison to 35mm in older patients >80 years.(98) Similar findings were also found in young black men <60 years.(104)

Table 1.9. Echocardiographic parameters in young adults with HF

Study		Age									
SHIFT(100) N=6505	Mean (SD) N EF, % All p<0.0001	<53 1522 28.4 (5.4)		53- <60 1521 29.1 (5.0)		60- <69 1750 28.9 (5.2)		≥69 1712 29.6 (5.0)			
DIAMOND study and ECHOS(101) N= 8507	% or mean N Wall motion index LVEF>45%	<65 1865 1.1 36		65-74 2769 1.3 45		75-84 3048 1.4 49		≥85 825 1.5 53		P <0.001 <0.001	
DIG study(87) N= 7788	Mean D N EF,%	<50 437 30.5	P 404 29.4	50-59 748 30.5	P 797 29.4	60-69 1465 31.8	P 1420 31.8	70-79 1013 33.1	P 1079 33.6	≥80 226 36.6	P 199 33.8
The Carvedilol Heart Failure Registry(95) N=4280	Mean (SD) N EF, % P<0.001	<55 806 30 (12)		55-64 922 30 (12)		65-75 1363 31 (12)		>75 1188 33 (13)			
DIAMOND study(98) N= 5419	% or median (5-95% percentile) N WMI≤ 1.2 WMI LVEDD (mm) p<0.001	<61 718 52 1.1 (0.5-1.9) 52 (35-67)		61-70 1481 45 1.2 (0.9-2.0) 50 (35-66)		71-80 2203 39 1.4 (1.0-2.0) 47 (35-63)		>80 1089 33 1.5 (1.0-2.0) 35 (32-60)			
French hospital survey(105) N=1058	% Echocardiography Ejection fraction <30% 30-39% 40-44% >45% p=0.001	27-68 87 32 22 18 28		68-78 83 26 23 13 38		78-86 74 11 25 16 48		86-100 64 12 25 15 48			
CHARM study(99) N=7599	Mean (SD) EF, % p<0.0001	<50 36 (14)		50-59 38 (14)		60-69 38 (15)		70-79 40 (15)		>80 43 (16)	
Val-HeFT(91) N= 5010	Mean N LVIDd/BSA, cm/m^2 *p=0.062; ^p<0.001	<65 2660 3.6				≥65 2350 3.7^					
V-HeFT I and II(102) N= 1446	Mean V-HeFT I N EF, % V-HeFT II N EF, % *p≤0.02	≤55 185 28 175 26		56-60 182 32 173 29		51-65 170 31 231 30		>65 105 30* 225 31*			
GWTG-HF(69) N=57937	N EF (%), median (IQR) EF<40% (% total cohort) Proportion with LV function documented *p<0.0001	≤65, 16245 30 (20-50) 56 93.8		66-77 12488 36 (25-55) 46 93.1		76-85 18398 40 (28-55) 39 92.8		>85 10806 45 (30-60)* 29* 89.4*			
Italian Network on Congestive Heart Failure Registry(96)	% N	≤65 AF 683	No AF 3578	66-75 AF 638	No AF 2013	≥75 AF 412	No AF 854				

N=8178	EF						
	>40%	27	21	35	23	41	34
	30-40%	37	40	42	46	43	44
	<30%	36	39	24	31	16	22
AREA IN-CHF study(89) N=467	Median (IQR)	<64			≥64		
	N	232			235		
	LVEF, %	40 (33-46)			41 (34-45)		
	LVEDV (ml/m^2)	80 (64-107)			77 (63-100)		
	LVESV (ml/m^2)	47 (36-67)			47 (37-61)		
	LV mass (g)	135 (106-163)			145 (118-167)*		
	E/A ratio	0.95 (0.75-1.20)			0.83 (0.67-1.22*)		
	Deceleration time (ms)	179 (134-228)			197 (141-257)^		
	*p<0.05; ^p<0.01						
Brooklyn heart failure clinic(104) N=108	Mean (SD)		<60			≥60	
		Black men		Black women	Black men		Black women
	EF, %	19.8 (1.2)		25.5 (2.0)	26.2 (2.4)		25.2 (2.2)
	LVEDD, cm	7.2 (0.1)		6.2 (0.3)	6.4 (0.2)		6.4 (0.2)

BSA=body surface area; D=Digoxin, EF=ejection fraction; LVEDD=left ventricular end diastolic diameter; LVEDV=left ventricular end diastolic volume; LVESV=left ventricular end systolic volume; LViDd=left ventricle internal diameter at diastole; LV=left ventricle; P= placebo; SD=standard deviation; WMI=wall motion index.

1.8 Renal function, haematological parameters and serum biomarkers in young adults with HF

Young adults with HF have lower serum creatinine(14;82;87-89;91;93;99;103;106;107), urea(14;82;91;93;108), brain natriuretic peptide(69;88;89;93;109), but higher haemoglobin,(69;82;99;106;107;109) and glomerular filtration rate (Table 1.10).(82;106) No significant different in mean serum sodium and potassium across age groups has been documented.(82;93) BNP and NT-pro BNP are lower in young adults (<65 years) compared to older patients.(69;88;89) There is no significant different in aldosterone level between young and older patients (dichotomised at 64 year of age).(89)

Table 1.10. Renal function, haematological parameters and serum biomarkers in young adults with HF

Study	Laboratory results	Age									
SHIFT(100) N=6505	Mean (SD) Creatinine clearance (mL/min/1.73kg/m^2) p<0.0001	<53 n=1522 87.4 (24.0)		53- <60 n=1521 79.0 (21.2)		60- <69 n=1750 71.0 (20.4)		≥69 n=1712 63.3 (19.1)			
DIG study(87) N= 7788	%	<50		50-59		60-69		70-79		≥80	
		D	P	D	P	D	P	D	P	D	P
	N	437	404	748	797	1465	1420	1013	1079	226	199
	Cr≥1.7 mg/dl	4	6	6	5	13	12	20	20	25	33
CARE HF(82) N=813	Median (IQR)	<60		60-70		>71					
	Haemoglobin (g/dl)	14.0 (13.1 to 15.1)		13.6 (12.6 to 14.8)		13.0 (11.9 to 14.2)					
	White blood cell count (x 10^9/L)	7.5 (6.3 to 9.2)		7.6 (6.3 to 9.0)		7.5 (6.1 to 9.1)					
	C reactive protein (mg/l)	6 (1 to 13)		6 (1 to 13)		8 (1 to 17)					
	Sodium (mmol/l)	138 (136 to 140)		138 (136 to 141)		139 (137 to 141)					
	Potassium (mmol/l)	4.2 (3.9 to 4.6)		4.4 (4.1 to 4.7)		4.5 (4.1 to 4.8)					
	Urea (mmol/l)	8.4 (5.9 to 15.0)		11.7 (7.4 to 19.3)		11.8 (8.4 to 18.9)					
	Creatinine (µmol/l)	94 (80 to 111)		106 (90 to 133)		118 (99 to 147)					
	Glomerular filtration rate (ml/min/1.73m^2)	72 (59 to 87)		60 (48 to 71)		49 (40 to 62)					
MERIT-HF(85) N=3991	Mean (SD)	<65				≥65					
		Placebo		Metoprolol CR/XL		Placebo		Metoprolol CR/XL			
	Serum Creatinine, ug/L	100 (28)		100 (27)		113 (37)		115 (37)			
CHARM study(99) N=7599	Mean (SD)	<50		50-59		60-69		70-79		>80	
	Kalaemia (mmol/L)	4.3 (0.5)		4.3 (0.4)		4.4 (0.5)		4.4 (0.5)		4.4 (0.5)	
	Haemoglobin (mmol/L)	14.2 (1.5)		13.9 (1.5)		13.6 (1.6)		13.3 (1.6)		13.2 (1.7)	
	Creatininemia (mg/dL)	1.1 (1.5)		1.1 (0.4)		1.2 (0.4)		1.3 (0.7)		1.3 (0.5)	
IMPROVE HF(93) N= 15381	Median (IQR)	≤64		65-76		>76					
	Sodium, mEq/L	139 (137-141)		140 (137-142)		140 (138-142)					
	BUN, mg/dL	18 (14-25)		22 (17-31)		26 (19-35)					
	Creatinine, mg/dL	1.1 (0.9-1.4)		1.2 (1.0-1.6)		1.3 (1.1-1.7)					
	BNP, pg/ml	254 (91.3-668.5)		383 (168-871)		546.5 (261-1080)					
	All p<0.001										
Val-HeFT(91) N= 5010	Mean	<65				≥65					
	N	2660				2350					
	Serum Creatinine, mg/dL,	1.2				1.4					
	Blood urea nitrogen, mg/dL	19.6				24.7					
DIG trial (103) N=7788	Mean (SD)	<65				≥65					
	N	3752				4036					
	Serum Creatinine (mg/dl)	1.2(0.3)				1.4(0.4)					
	Serum potassium (mEq/l)	4.3(0.4)				4.4(0.4)					
GWTG-HF(69) N=57937	Median, IQR	≤65, %		66-77, %		76-85, %		>85, %			
	Cr (mg/dL)	1.3 (1.0-1.9)		1.4 (1.0-2.0)		1.4 (1.0-1.9)		1.3 (1.0-1.8)			
	Hb (g/dL)	12.5 (10.9-14.1)		12.0 (10.6-13.5)		11.9 (10.5-13.2)		11.8 (10.5-13.1)			
	BNP (pg/ml)	814 (384-1690)		815 (398-1650)		849 (453-1646)		872 (468-1648)			
	Troponin (ng/ml)	0.05 (0.03-0.10)		0.05 (0.03-0.11)		0.05 (0.03-0.11)		0.06 (0.03-0.12)			
Italian Network on Congestive Heart Failure Registry(96) N=8178	%	≤65				66-75				≥75	
		AF	No AF	AF	No AF	AF	No AF				
	N	683	3578	638	2013	412	854				
	Potassium <3.5mEq/l	2.4	1.6	3.7	2.0	4.2	1.4				
	Creatinine>2.5mg/dl	1.4	2.1	2.3	3.6	1.8	5.4				

AREA IN-CHF study(89) N=467	Median (IQR)	<64		≥64	
	Creatinine (mg/dl)	1.00 (0.90-1.15)		1.10 (0.90-1.30)*	
	Creatinine clearance (ml/min)	88 (77-109)		65 (54-81)^	
	Potassium (mmom/l)	4.4 (4.1-4.6)		4.4 (4.1-4.7)	
	BNP (pg/ml)	52 (23-129)		116 (62-216)^	
	Aldosterone (pg/ml)	124 (80-191)		113 (70-167)	
	*p<0.001; ^p<0.0001				
PRIME-II study(88)		38-62	63-69	70-73	74-80
N=311	Creatinine (µmol/l), mean (SD)	107 (31)	114 (33)	120 (32)	130 (50)
	Natriuretic peptide (median [min-max])				
	ANP (pmol/l)	88 (12-597)	103 (19-508)	115 (18-720)	105 (28-815)
	NT-ANP (pmol/l)	689 (129-3414)	1066 (256-3081)	1151 (239-4210)	1148 (344-3760)
	BNP (pmol/l)	33 (0.6-352)	47 (3-322)	79 (1.4-502)	65 (7.6-373)
	NT-proBNP (pmol/l)	372 (3-2928)	527 (5-3380)	711 (3-5295)	715 (14-4820)

ANP= Atrial Natriuretic Peptide; BNP=B-type Natriuretic Peptide; BUN=blood urea nitrogen; D=Digoxin, IQR=interquartile range; NT-ANP=N-terminal Atrial Natriuretic Peptide; NT-proBNP= N-terminal pro B-type Natriuretic Peptide; P= placebo; SD=standard deviation;

1.9 Baseline medications in young adults with HF

Young adults (<65 years) with HF are more likely to be on a beta-blocker, ACE inhibitor or ARB, and aldosterone antagonist (Table 1.11). They are also prescribed higher doses of beta-blocker and aldosterone antagonist.(82;100) Younger adults require less diuretics and in smaller doses.(33;82;100) The use of digitalis in younger adults is conflicting with some older studies reported lower prescription rate,(33;94) but more contemporary series reported higher use of digoxin in younger adults.(82;100)

Table 1.11. Baseline medications in young adults with HF

Study	Medications (%)	Age			
SHIFT(100)		<53	53- <60	60- <69	≥69
N=6505	N	1522	1521	1750	1712
	Beta blocker (all)	93	92	89	85
	At least half target dose	53	54	48	41
	At target dose	27	26	22	18
	ACE inhibitors	78	81	79	77
	ARB	14	12	15	16
	Diuretics	82	81	84	86
	Antialdosterone agents	68	62	59	54
	Cardiac glycosides	30	23	18	17
	all statistical significant				
IMPROVE HF(93)		≤64	65-76	>76	
N= 15381	N	5307	5176	4791	
	ACEi/ARB	84	80	73*	
	B-blocker	90	86	81*	
	Aldosterone antagonist	46	34	27*	
	Anticoagulation	71	71	68	
	*p<0.001				
GWTG-HF(69)		≤65, %	66-77, %	76-85, %	>85, %
N=57937	N	16245	12488	18398	10806
	ACEi/ARB	89	84	82	79*
	Beta-blocker	91	88	88	83*
	Aldosterone antagonist	29	25	21	18*
	*p<0.0001				
HF ACTION		<60	60-69	≥70	
study(84)	N	1214	640	477	
N=2331	ACEi/ARB	96	94	92*	
	B-blocker	96	94	91^	
	*p=0.01;^p<0.001				
InSync/InSync ICD		<65	65-74	≥75	
Italian Registry(97)	N	571	740	476	
N= 1787	ACEi/ARB	79	71	70*	
	Beta-blocker	60	45	37*	
	Digoxin	43	43	45	
	Diuretics	87	89	88	
	Nitrates	17	23	26*	
	Class III antiarrhythmic drug	34	38	34	
	*Statistically significant				
Taiwan(10)		20-64	≥65	All	
N= 2692	N	567	2125	2692	
	ACEi and/or ARB	58	49*	51	
	CCB	29	29	29	
	Beta blocker	35	23*	25	
	Diuretic	74	77	76	
	Aspirin	39	42	41	
	Clopidogrel	12	13	13	
	Digoxin	29	33	32	
	Warfarin	7	5*	5	
	*Statistically significant				
CARE HF(82)		<60	60-70	>71	
N=813	N	219	315	277	
	Diuretic All	99	99	99	
	Loop diuretics	90	95	97	
	Proportion taking ≥80mg of furosemide or equivalent	37	46	46	
	Thiazide (or related) diuretic	16	18	11	

	Proportion on loop/thiazide combination			11		14			9		
	Spironolactone			63		57			50		
	Spironolactone at least 25mg daily			60		49			43		
	Other diuretics			6		7			4		
	ACE inhibitor			85		81			74		
	ACE inhibitor at least half target dose			50		38			28		
	ARB			13		18			18		
	ACEi or ARB			97		96			92		
	Beta blockers			84		71			64		
	Beta blocker at least half target dose			53		36			34		
	Digitalis			49		47			33		
	Amiodarone			12		19			19		
	Other antiarrhythmic agents			1		0			0		
	Nitrate			20		33			40		
	Calcium channel blocker			4		4			8		
	Insulin			8		14			9		
	Oral hypoglycaemic			9		14			9		
	Insulin + oral hypoglycaemic			1		2			1		
	Statins			39		41			39		
	Other lipid lowering			9		6			8		
	Anticoagulants			41		36			27		
	Aspirin			33		42			55		
	Other antiplatelet			4		8			8		
	Other NSAIDS			1		2			4		
	Allopurinol			16		20			18		
Kent, Surrey and Sussex Primary Care Research Network(33) N= 2129		45-54		55-64		65-74		75-84		85+	
		M	W	M	W	M	W	M	W	M	W
	ACEi	90	82	86	69	82	72	78	75	63	61
	Loop diuretics	65	64	71	71	76	84	84	82	83	83
	Thiazide diuretics	25	27	51	46	51	49	52	57	54	57
	Spironolactone	10	9	21	17	21	17	15	13	14	12
	Digoxin	15	0	37	21	31	25	39	32	31	39
	Aspirin	80	55	72	42	68	60	64	60	68	60
	Lipid lowering agents	55	27	62	33	51	44	29	28	4	7
Spanish national survey(110) N= 2145		<65		65-80		>80					
	N	226		1038		881					
	on admission										
	Diuretics	66		69		68					
	Spironolactone	18		18		12					
	ACEis, low dose	31		32		28					
	ACEis, appropriate dose	10		13		9					
	Beta-blockers	16		10		5					
	Digoxin	28		33		32					
	Nitrates	18		26		33					
	ARAII	7		7		4					
	Anticoagulants	32		31		12					
	Amiodarone	5		8		7					
	Amlodipine	6		9		6					
	on discharge										
	Diuretics	86		86		84					
	Spironolactone	38		32		25					
	ACEis, low dose	36		40		42					
	ACEis, appropriate dose	28		23		17					
	Beta-blockers	18		8		6					
	Digoxin	35		40		38					
	Nitrates	27		33		40					
	ARAII	7		7		5					
	Anticoagulants	41		36		17					
	Amiodarone	8		9		8					
	Amlodipine	10		9		7					
MERIT-HF(85) N=3991		<65				≥65					
		Placebo		Metoprolol CR/XL		Placebo		Metoprolol CR/XL			
	N	1009		1000		992		990			
	Diuretics	89		89		91		93			

	ACE inhibitors	91		91		87		87*		
	ACE inhibitors or AII blocker	97		97		95		94*		
	Digitalis	66		64		62		63		
	Aspirin	43		43		49		48*		
	Statin	25		24		23		21*		
	*Statistically significant									
DIAMOND study and ECHOS(101) N= 8507		<65		65-74		75-84		≥85		All
	N	1865		2769		3048		825		8507
	ACEi	64		55		48		38		53
	Beta-blocker	42		35		33		29		35
	Diuretics	85		88		90		89		88
	Digoxin	44		49		48		46		47
	All statistically significant									
IMPROVEMENT of HF survey(94) N=8256		<65		65-74		75-84		≥85		All
		M	F	M	F	M	F	M	F	M	F
	ACEi/ ARB	69	68	72	71	67	68	57	65	69*	69
	B-blocker	44	35	31	31	23	23	14	12	33*	27*
	ACEi/ ARB and B-blocker	30	25	22	23	15	15	8	8	22*	19*
	Loop or thiazides diuretics	61	70	72	79	81	83	88	86	71*	79*
	Spironolactone	11	13	13	13	15	17	16	15	13*	15*
	Digitalis	33	39	41	45	41	48	49	50	38*	45*
	Antiplatelet drug	68	56	64	56	56	54	62	55	63*	56
	Oral anticoagulant	19	16	24	18	23	16	14	7	21	15*
	*Statistically significant										
French hospital survey(105) N=1058		27-68		68-78		78-86		86-100		
	ACE inhibitors	82		67		60		49*		
	Diuretics	91		93		92		88^		
	Digitalis	40		39		35		34`		
	*p=0.001; ^p=0.3; `p=0.5									
DIAMOND study(98) N= 5419		<61		61-70		71-80		>80		
	N	718		1481		2203		1089		
	ACE inhibitor	62		56		50		38*		
	Digoxin	49		51		53		55^		
	Beta-blocker	15		15		13		8*		
	Diuretics	79		86		86		87*		
	*p<0.001; ^p=0.05									
DIG study(87) N= 7788		<50		50-59		60-69		70-79		≥80	
		D	P	D	P	D	P	D	P	D	P
	N	437	404	748	797	1465	1420	1013	1079	226	199
	Diuretics	77	75	79	78	79	82	85	86	89	92
	ACEi	94	96	92	96	93	94	94	92	93	91
	D=digoxin; P=placebo.										
The Carvedilol Heart Failure Registry(95) N=4280		<55		55-64		65-75		>75		
	N	806		922		1363		1188		
	ACEi	81		79		74		69*		
	Diuretic	72		75		77		81*		
	Digoxin	59		58		57		56^		
	*p<0.001; ^p=0.300									
PRIME-II study(88) N=311				38-62		63-69		70-73		74-80	
	N			76		77		67		91	
	ACE inhibitors			96		96		97		92	
	Diuretics			96		100		99		99	
	Digoxin			50		68		63		58	
	Anti-arrhythmic			20		21		13		18	
	Beta-blockers			12		8		15		8	
BEST(92) N= 2708		<65				≥65					
		Bucindolol		Placebo		Bucindolol		Placebo			
	N	821		795		533		559			
	ACE inhibitor	93		92		89		89*			
	Angiotensin II antagonist	5		7		7		7			
	Digitalis	93		93		91		91			
	Diuretic	94		93		94		94			
	Spironolactone	4		4		2		4			
	Vasodilator	42		45		53		52*			

	Hydralazine/Isosorbide dinitrate	31	33	39	36*	
	Antiarrhythmic	3	2	5	3	
	Anticoagulant	45	49	42	41	
	Aspirin	41	41	49	51*	
	Statin	21	23	25	24	
	*Statistically significant					
CHARM study(99)		<50	50-59	60-69	70-79	>80
N=7599	N	605	1474	2351	2474	695
	Beta blocker	64	63	58	50	42*
	Diuretics	77	78	82	85	92*
	ACEi	49	46	44	37	27*
	Spironolactone	19	15	17	17	18
	Anticoagulation	28	29	30	33	30*
	Antiplatelet	51	62	64	60	56*
	Lipid lowering agents	38	47	45	41	23*
	*Statistically significant					
Val-HeFT(91)		<65		≥65		
N= 5010	N	2660		2350		
	ACEi	95		90*		
	Beta blocker	40		29*		
	Diuretics	83		88^		
	Digoxin	68		66		
	Calcium channel blocker	11		14*		
	Spironolactone	6		4		
	*p<0.001,^p=0.001					
DIG trial (103)		<65		≥65		
N=7788	N	3752		4036		
	ACEi	94		93*		
	Hydralazine and nitrates	1		1		
	Diuretics	75		81*		
	Potassium-sparing diuretics	8		7		
	Potassium supplement	27		29*		
	*statistically significant					
Italian Network on		≤65		66-75		≥75
Congestive Heart		AF	No AF	AF	No AF	AF	No AF
Failure Registry(96)	N	683	3578	638	2013	412	854
N=8178	B-blocker	18	25	11	17	5	8
	ACEi	84	86	77	80	71	74
	Digoxin	89	59	84	57	84	56
	Oral anticoagulant	72	24	58	17	27	9
	Aspirin	13	34	23	43	37	43
	Other antiarrhythmic	29	24	25	26	20	23
	Diuretics	92	78	92	85	90	85
AREA IN-CHF		<64		≥64		
study(89)	N	232		235		
N=467	ACEi	79		80		
	ARBs	18		18		
	ACEi or ARB	96		96		
	B-blocker	85		73*		
	Furosemide	53		68*		
	Thiazides	4		5		
	Nitrates	19		34*		
	Amiodarone	16		19		
	Aspirin	46		49		
	Statins	49		41		
	Dihydropyridines	5		1		
	Calcium antagonist	0		1		
	*p<0.01					

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; DIG=Digitalis Investigation Group.

1.10 Demographic and physiological parameters in young adults with HF

In young adults with HF, there is higher proportion of non-Caucasians in randomised clinical trials and registries from North America (Table 1.12). Younger adults have higher heart rate and diastolic blood pressure, but a lower systolic blood pressure. Young adults also have a higher body mass index (BMI) and a higher proportion of them are obese (BMI≥30kg/m^2).

1.11 Precipitating factors for HF hospitalisations in young adults with HF

A study from Spain found no difference in precipitating factors for HF hospitalisations between those aged 40-74 years, and those aged 75 years and over.(111). To date no study has examined patients less than 40 years of age.

1.12 Hospitalisation cost in young adults with HF

Younger patients have a higher hospitalisation cost. Odds ratio for cost was: aged 19-64 years OR 1.24 (95% CI: 1.18-1.29); aged 65-74 years OR 1.31 (95% CI: 1.25-1.37) and aged ≥85 years OR 0.44 (95%CI: 0.41-0.47) with age group 75-84 years as the referent group.(112) Younger patients (20-64 years) have higher fees in surgery, anaesthesia, haemodialysis, and blood or plasma compared to those aged ≥65 years.(10) With the increasing use of cardiac device therapy and ventricular assist device in young adults, the cost of managing young adults with HF is increasing.

Table 1.12. Demographic and physiological parameters

Study		Age			
SHIFT(100)	Mean (SD)	<53	53- <60	60- <69	≥69
N=6505	N	1522	1521	1750	1712
	HR (b.p.m)	81(10)	80.5(10)	80(9)	79(29)
	SBP (mmHg)	118(16)	122(16)	122(16)	124(16)
	DBP (mmHg)	76(10)	77(10)	75(9)	75(9)
	p<0.0001				

DIG study(87) N= 7788	Mean	<50		50-59		60-69		70-79		≥80	
		D	P	D	P	D	P	D	P	D	P
	HR (b.p.m)	81	82	81	82	78	78	77	78	78	78
	SBP (mmHg)	121	122	121	122	128	128	131	130	132	130
	D=Digoxin, P= placebo										

BEST(92) N= 2708	% or mean(SD)	<65		≥65	
		Bucindolol	Placebo	Bucindolol	Placebo
	N	821	795	533	559
	African-American	28	27	17	16
	Heart rate	84(14)	83(14)	78(12)	78(12)
	SBP	116(18)	116(18)	119(18)	119(18)
	All statistically significant				

V-HeFT I and II(102) N= 1446	Mean	≤55	56-60	51-65	>65
	V-HeFT I				
	N	185	182	170	105
	HR (b.p.m.)	85	81	83	79*
	SBP (mmHg)	115	120	120	125*
	DBP (mmHg)	77	76	75	75
	V-HeFT II				
	N	175	173	231	225
	HR (b.p.m.)	81	78	78	75*
	SBP (mmHg)	121	125	127	131*
	DBP (mmHg)	80	78	78	75*
	*p≤0.02				

Greater Worcester hospital(113) N=3722	%	<65	65-74	75-84	≥85
	BMI (kg/m^2)				
	<18.5	9	18	33	41
	18.5-24.9	8	18	44	30
	25.0-29.9	14	27	38	21
	30.0-34.9	18	30	38	15
	≥35.0	39	26	27	7
	P<0.001				

HF ACTION study(84) N=2331	% or median(IQR)	<60	60-69	≥70
	Total number	1214	640	477
	Black	42	25	19*
	White	52	69	79*
	Other	6	6	3*
	Weight (kg)	97(79-114)	88(77-102)	82 70-93)
	BMI (kg/m^2)	32(27-38)	29(26-33)	27(24-31)*
	HR at rest	72(64-80)	68(62-75)	68(60-75)*
	SBP (mmHg)	110(100-122)	112(102-127)	118(104-130)*
	DBP (mmHg)	70(62-80)	70(60-78)	68(60-76)*
	*p<0.001			

MERIT-HF(85) N=3991	% or mean(SD)	<65		≥65	
		Placebo	Metoprolol CR/XL	Placebo	Metoprolol CR/XL
	N	1009	1000	992	990
	Caucasian	92	92	97	96
	SBP (mmHg)	128(16)	129(16)	132(18)	132(18)
	DBP (mmHg)	80(9)	80(9)	77 (9)	77(9)
	HR (b.p.m)	84(10)	84(10)	81 (10)	81(10)
	BMI (kg/m^2)	28(5)	28(5)	27(4)	26(4)
	All statistically significant				

The	% or mean (SD)	<55	55-64	65-75	>75

Carvedilol Heart Failure Registry(95) N=4280	N	806	922	1363	1188
	Black	22	13	10	8*
	Heart rate	82 (15)	78 (14)	76 (13)	75 (13)*
	SBP	126 (21)	128 (20)	129 (20)	131 (21)*
	DBP	78 (13)	76 (11)	74 (11)	71 (12)*
	*p<0.001				
CARE HF(82) N=813	% or mean SD	<60	60-70	>71	
	N	219	315	277	
	BMI (kg/m^2)	28(25-31)	28(24-30)	26(23-29)	
	BMI >30, %	31	25	16	
	BMI <20, %	4	7	12	
	Heart rate (bpm)	70 (60-77)	72 (62-80)	69 (60-78)	
	Lying SBP (mmHg)	115 (102-125)	117 (104-129)	121 (110-130)	
	Lying DBP (mmHg)	71 (65-80)	71 (60-80)	69 (60-80)	
	Standing SBP (mmHg)	112 (100-120)	112 (100-125)	116 (100-126)	
	Standing DBP (mmHg)	72 (65-80)	70 (60-80)	68 (60-78)	
CHARM study(99) N=7599	Mean (SD)	<50	50-59	60-69	70-79	>80
	SBP (mmHg)	125 (18)	128 (18)	130 (19)	134 (19)	135 (20)
	DBP (mmHg)	79 (11)	78 (10)	77 (11)	76 (11)	74 (11)
	P<0.001					
IMPROVE HF(93) N= 15381	% or median (IQR)	≤64	65-76	>76	
	N	5307	5176	4791	
	SBP (mmHg)	120 (107-130)	120 (109-131)	120 (110-132)*	
	HR (b.p.m)	72 (65-80)	70 (64-78)	70 (64-77)*	
	*p<0.001				
Val-HeFT(91) N= 5010	% or mean	<65	≥65		
	N	2660	2350		
	White	87	94		
	SBP (mmHg)	121	127		
	DBP (mmHg)	77	74		
	Pulse (b.p.m.)	74	73		
	All p<0.001				
DIG trial (103) N=7788	% or mean (SD)	<65	≥65		
	N	3752	4036		
	Non-white	18	11		
	BMI (kg/m^2)	28 (6)	26 (5)		
	HR (b.p.m)	79 (13)	77 (12)		
	SBP (mmHg)	125 (20)	130 (21)		
	DBP (mmHg)	76 (11)	74 (11)		
	All p<0.0001				
GWTG-HF(69) N=57937	%	≤65 n= 16245	66-77 n= 12488	76-85 n= 18398	>85 n= 10806
	Race				
	Caucasian	52	70	81	84
	African American	32	16	8	6
	p<0.0001				
North American centers(90) N=546	% or mean (SD)	<65	≥65		
	N	328	218		
	Caucasian	63	75*		
	BMI	31 (7)	27 (5)^		
	*p=0.005; ^p<0.001				
AREA IN-CHF study(89) N=467	Median (IQR)	<64	≥64		
	N	232	235		
	BMI (kg/m^2)	27(25-30)	26(24-29)*		
	SBP (mmHg)	125(113-138)	130(120-140)*		
	DBP (mmHg)	80(70-80)	80(70-80)		
	Heart rate (bpm)	65(60-72)	66 (60-75)		
	*p<0.01				
Brooklyn heart failure clinic(104) N=108	Mean (SD)	<60		≥60	
	BMI (kg/m^2)	Black men 33(2)	Black women 30(2)	Black men 26(1)	Black women 27(2)
PRIME-II study(88) N=311	Mean (SD)	38-62	63-69	70-73	74-80
	N	76	77	67	91
	SBP (mmHg)	125(18)	123(17)	123(19)	126(18)
	DBP (mmHg)	73(8)	75(9)	75(10)	76(9)
	Heart rate (bpm)	81(17)	81(15)	81(15)	81(14)
DIAMOND study and	Mean	<65	65-74	75-84	≥85	All
	N	1865	2769	3048	825	8507

ECHOS(101) N= 8507	BMI (kg/m^2) p<0.0001	28	26	25	24	26

BMI=body mass index; b.p.m=beats per minute; DBP=diastolic blood pressure; HR=heart rate; IQR=interquartile range; SBP=systolic blood pressure; SD=standard deviation;

1.13 Prevalence of venous thrombo-embolism in young adults with HF

Young adults (<40 years) who were hospitalised with HF have the highest prevalence of documented pulmonary embolism (1.15% in <40 years, 1.01% in 40-59 years, 0.82% in 60-79 years, and 0.69% in >80 years) and deep vein thrombosis (1.68% in < 40 years, 1.33% in 40-59 years, 1.10% in 60-79 years, and 1.24% in >80 years) and decreases with age.(114)

1.14 Quality of life in young adults with HF

Compared to older patients, younger adults (<65 years) with HF have a worse quality of life (QOL) in both emotional and physical components of the Minnesota Living with Heart Failure (MLwHF) Questionnaire (Table 1.13).(91;115-117) Studies using other methods of assessing QOL reported similar findings.(82;90) Younger adults (<65 years) with HF have poorer mental and general health when measured using Short-Form (36) Health Survey.(117)

1.15 HF Education in young adults with HF

Younger adults with HF are more likely to receive HF education (66.2% in ≤64 years, 60.6% in 65-76 years and 57.3% in >76 years, p<0.0001).(93)

1.16 Influenza immunisation in young adults with HF

In contrast to most HF interventions, influenza immunisation rates are lower in younger adults with HF.(33) In one study conducted in Kent, Surrey, and Sussex using the primary care research network, 60% and 70% of patients aged 45-54 and 55-64 years had

influenza immunisation in comparison 84.8%, 88.6%, and 92.3% of patients aged 65-74, 75-84, and ≥85 years, respectively.(33)

Table 1.13. Quality of life in young adults with HF

Study	Quality of life				
Urban county hospital outpatient clinics(116) N= 165	Mean (SD)	Men, <65	Men, ≥65	Women, <65	Women, ≥65
	Chronic heart failure questionnaire				
	Total scale	4.3 (0.14)	5.1 (0.31)	3.6 (0.14)	4.3 (0.22)
	Dyspnoea	4.3 (0.17)	5.4 (0.38)	3.9 (0.19)	4.3 (0.26)
	Fatigue	3.8 (0.16)	4.2 (0.41)	3.2 (0.17)	3.8 (0.27)
	Emotional	4.6 (0.15)	5.4 (0.31)	3.8 (0.16)	4.6 (0.22)
	Living with heart failure questionnaire				
	Total scale	40.9 (3.2)	30.0 (5.5)	51.4 (3.8)	38.3 (4.8)
	Physical	18.5 (1.5)	15.6 (2.8)	23.0 (1.7)	18.3 (2.3)
	Emotional	8.9 (0.9)	4.4 (1.1)	12.2 (1.2)	9.1 (1.4)
Outpatient academic HF practice, Baltimore, Maryland(117) N=155	Mean (SD)	≤64	>64	p value	
	SF-36 subscale				
	Physical functioning	31.8 (11.9)	32.4 (1.4)	0.74	
	Role-physical	34.8 (11.4)	35.0 (1.3)	0.90	
	Bodily pain	40.4 (12.5)	45.5 (1.4)	0.015	
	General health	33.2 (11.3)	36.9 (1.4)	0.053	
	Vitality	42.9 (11.7)	45.7 (1.4)	0.15	
	Social functioning	39.7 (13.2)	42.9 (1.6)	0.15	
	Role-emotional	38.9 (13.3)	41.1 (1.6)	0.32	
	Mental health	44.6 (15.0)	50.2 (1.4)	0.014	
	MLwHF scale				
	Total	46.0 (27.72)	32.7 (24.0)	0.0002	
	Emotional component	8.9 (8.0)	6.1 (6.5)	0.022	
	Physical component	20.1 (12.6)	15.6 (14.4)	0.042	
Val-HeFT(91) N= 5010	Mean	<65	≥65		
		N= 2660	N= 2350		
	MLHFQ overall score	35.7	28.7		
North American centers(90) N=546	Mean (SD)	<65	≥65		
	N	328	218		
	KCCQ HRQL Score	54 (28)	60 (25)		
A-HeFT(118) N=1050	Mean (SD)	<65	≥65		
	MLHFQ overall score	55.0 (20.8)	41.0 (19.0)		

HRQL=health related quality of life; KCCQ=Kansas City Cardiomyopathy Questionnaire; MLwHF=Minnesota Living with Heart Failure Questionnaire; SD=standard deviation

1.17 Pharmacological treatment of HF in young adults with HF

1.17.1 Angiotensin-neprilysin inhibitor

The effect of angiotensin-neprilysin inhibitor on mortality and morbidity (dichotomised at 65 years of age) were independent of age.(119;120)

1.17.2 Angiotensin Converting Enzyme Inhibitor

Landmark trials including the effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),(121) the Results of the Treatment Trial of the Studies of Left Ventricular Dysfunction (SOLVD),(122) and the effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions trial,(123) did not report age interaction.

1.17.3 Beta-Blocker

In the Metoprolol CR/XL Randomised Intervention Trial in Chronic Heart Failure (MERIT-HF) trial, the effects of metoprolol CR/XL on all-cause mortality, all-cause mortality or all-cause hospitalisation, and sudden death were independent of age (dichotomised at 65 years of age).(85) Similarly, the effects of carvedilol on mortality in the effect of carvedilol on morbidity and mortality of patients with chronic heart failure: the U.S. Carvedilol Heart Failure Study Group trial (dichotomised at 59 years), the mortality of patients with severe chronic heart failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study (dichotomised at 65 years of age), were also independent of age.(124;125)

1.17.4 Angiotensin receptor blocker

The effects of valsartan, losartan, and candesartan on mortality and morbidity outcomes in patients with HF are independent of age. The Valsartan Heart Failure Trial (Val-HeFT)(126), and the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study dichotomised at 65 years (127), and the CHARM programme stratified patients into 5 age groups (<50, 50-59, 60-69, 70-79, and ≥80 years)(99), did not show any interaction between age and outcomes.

1.17.5 Mineralocorticoid Receptor Antagonist

The effects of spironolactone and eplerenone on all-cause mortality are independent of age. The Randomised ALdactone Evaluation Study (RALES) dichotomised at 67 years (128), and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) dichotomised at <65 years (129), showed the benefits of spironolactone and eplerenone were independent of age.

1.17.6 Ivabradine/ Digoxin

In a post-hoc analysis from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), there was significant interaction between age groups (<53, 53-<60, 60-<69, and ≥69 years) and primary end point (cardiovascular death or hospital admission for worsening heart failure) [p for interaction= 0.038], as well as secondary end points of hospital admission for worsening heart failure [p for interaction= 0.019] and heart failure death [p for interaction= 0.013].(100) Patients aged <53 years benefited more from the treatment of ivabradine.

There was no interaction between age and the treatment with digoxin on the composite end point in the DIG study.(87)

1.17.7 Hydralazine and Isosorbide Dinitrate

The benefits of hydralazine and Isosorbide dinitrate on survival did not have any significant age interaction.(102)

1.18 Device therapies of HF and heart transplantation in young adults with HF

1.18.1 Implantable Cardioverter Defibrillator (ICD)/ Cardiac Resynchronisation Therapy (CRT)

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) comparing ICD group with placebo showed younger patients <65 years of age had more to gain from ICD therapy [HR for all-cause mortality 0.68(0.50-.93) in <65 years vs. HR 0.86(0.62-1.18) in >65 years].(130) In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), the benefits of ICD in reducing all-cause mortality were independent of age.(131)

The Multicenter InSync Randomised Clinical Evaluation (MIRACLE) and the Multicenter InSync ICD Randomised Clinical Evaluation (MIRACLE-ICD) trials enrolled patients with NYHA class III/IV, ejection fraction ≤35% and QRS duration of ≥130msec and stratified them into three age groups (<65 years, 65-75 years, and >75 years) reported the effects of CRT on the improvement of NYHA functional class and left ventricular ejection fraction were independent of age.(132)

The effects of CRT on morbidity and mortality were independent of age in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial(133), the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronisation Therapy (MADIT-CRT)(134), the Resynchronisation-Defibrillation for Ambulatory Heart Failure Trial (RAFT)(135), the Cardiac Resynchronisation-Heart Failure (CARE-HF) study(82), the CARE-HF extension phase

study,(136), and the REsynchronisation reVErses Remodelling in Systolic left vEntricular dysfunction (REVERSE) study(137).

Younger patients are more likely to have CRT (≤65 years: 2.1% vs. >85 years: 0.6%, p<0.0001) and implantable cardioverter defibrillator (≤65 years: 5.5% vs. >85 years: 0.4%, p<0.0001) during their incident HF hospitalisation.(69) The use of ICD and/or CRT-D are higher in younger patients (ICD or CRT therapy: 51.8% in ≤64 years, 56.5% in 65-76 years and 43.0% in >76 years, p<0.001).(93)

1.18.2 Ventricular Assist Devices (VAD)

The Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH) study randomised 129 patients with end-stage HF who were ineligible for cardiac transplantation to implantation of a left ventricular assist device (LVAD) or optimal medical management.(138) LVAD reduced the risk of all-cause mortality. Subgroup analysis by age stratification (18-59 years, 60-69 years and ≥70 years) showed a significant reduction in the risk of death in patients aged 60-69 years with a LVAD compared to medical therapy (RR 0.49, 95%CI: 0.25-0.95). In the younger patients aged 18-59 years (RR 0.47, 95%CI: 0.17-1.28) and older patients aged ≥70 years (RR 0.59, 95%CI: 0.31-1.15), there were a trend towards lower risk death.

In the 6th INTERMACS annual report, patients aged <50 and 50-64 years have a better survival after continuous flow VAD implantations compared to those aged ≥65 years.(139)

1.18.3 Heart transplantation

Heart transplantation should be considered in patients aged ≤70 years with end-stage HF.(140;141) Although age is strictly not a contraindication to heart transplantation,

very few patients in the UK are transplanted above the age of 65 years.(7) A pragmatic age restriction to patients under 65 to 70 years has been justified for two reasons: 1) limited donor pool, and 2) increasing mortality with increasing age.(142)

In 2006-2012, 16% and 45% of those who had a cardiac transplantation were aged 18-39 and 40-59 years, respectively.(143) Cardiomyopathy remains as the main diagnosis for heart transplant up to age 59 years (74% in 18-39 years, 55% in 40-59 years, 40% in 60-69 years, and 37% in ≥70 years; $p<0.0001$). Patients aged 18-39 years were most likely to be hospitalised at time of transplant (18-39 vs. ≥70 years: 51% vs. 40%; $p<0.0001$), be on intravenous inotropes (46% vs. 40%; $p=0.0083$), and supported by left ventricular assist device (30% vs. 18%; $p<0.0001$), right ventricular assist device (5.7% vs. 1.3%; $p<0.0001$), total artificial heart (1.1% vs. 0.0%; $p=0.0140$), or extracorporeal membrane oxygenation (2.1% vs. 0.0%; $p<0.0001$). Median survival is also highest in young adults aged 18-39 years (12.6 years in 18-39 years, 10.7 years in 40-59 years, 9.1 years in 60-69 years, and 8.2 years in ≥70 years). Young adults aged 18-39 years are more likely to die of cardiac allograft vasculopathy, acute rejection, graft failure, but less likely to die of malignancy, infection, multi-organ failure, or renal failure.(143)

1.19 Conclusion

The incidence and prevalence of HF in younger adults is lower compared to older age group. Unlike the older age groups where the incidence of HF continues to decline, the incidence in younger adults remains static with some studies suggesting that it is on the rise. Little is known about the incidence and prevalence of HF in young adults outside Europe and the North America. Mortality and HF hospitalisation in younger adults have seen little change in recent decade. Aetiology and co-morbidities of HF in young adults are poorly understood. Clinical presentation is also different in young adults. Further research of HF in young adults may help to understand and manage them better.

1.20 Aim of the thesis

Review of the literature demonstrated the lack of data in younger adults with HF especially those <40 years of age. Limited contemporary studies reported incidence of HF and trends in young adults with HF. Using a large linked hospital, outpatient and emergency department administrative database, I aim to explore the incidence of HF and its trends in young adults with HF.

Similarly, no contemporary studies reported long-term mortality in young adults with HF. I aim to examine the long-term mortality and its trend in young adults with HF using a primary care and a secondary care linked hospital, outpatient and emergency department administrative databases.

The understanding of how young adults with HF present with decompensated HF is also lacking. I aim to explore this using a randomised clinic trial dataset with detail documentation of patients' symptoms and signs of HF and the precipitating factors leading to their HF hospitalisations.

Along with examining how young adults with decompensated HF present to hospital, I will also explore what happen following their discharge from hospital using a linked hospital, outpatient and emergency department administrative database. The linked dataset allows me to examine how young adults with HF interact between outpatient clinic or emergency department and hospital admission.

In summary, the aim of the thesis is to examine the characteristics of young adults with HF and their short and long term outcomes in a variety of different HF populations: a randomised clinical trial population; a meta-analysis consisted of patients from large HF registries, observation studies, and randomised trials; a primary care database which is the largest in the world; and a hospital administrative database with linked hospital, outpatient clinics, and emergency department databases.

1.21 Objectives

In the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity programme (CHARM) study,

- To describe the baseline characteristics of patients with HF by age
- To examine the aetiology of HF by age
- To describe the symptoms and signs of HF by age
- To examine the differences in electrocardiograph and chest radiograph by age
- To describe the quality of life measured by Minnesota Living with HF score by age
- To determine the HF hospitalisation rates by age
- To determine the mortality rates of patients with HF in a clinical trial

In the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) study,

- To describe the baseline characteristics of patients with HF by age
- To examine the aetiology of HF by age
- To determine the prognosis of HF by age and ejection fraction in clinical trials and observational studies

In the U.K. Clinical Practice Research Datalink (CPRD) study,

- To describe the baseline characteristics of patients with HF by age
- To examine the prescription rates of HF medications by age
- To determine the mortality rates by age and by year

In the Alberta Ministry of Health and Wellness database,

- To describe the baseline characteristics of patients with HF by age
- To determine the incidence of first HF hospitalisation by age
- To determine the non-fatal outcomes following index HF hospitalisation
- To determine the mortality rate by age

Chapter 2

Methods

2.1 Introduction

The methods of each study are described in each individual chapter in detail. The following describe the statistical tests that are common to all the chapters.

2.2 Analysis of Variance

The one-way analysis of variance is used to compare means from three or more categories. It is based on variability between the group means. The 'between group variance' is the variability between the group means, and the 'residual variance' is the variability not due to the differences between the group. The ratio of the two variance is the F ratio, which follows the F distribution. The F ratio corresponds to the P value. $P < 0.05$ is indicating the group means are different from each other.

The test has two assumptions. Firstly, the continuous data are normally distributed within each group. The second, each group must have equal variance (standard deviation). Data were assessed to ensure that these assumptions were not violated.

2.3 Chi-squared test

The chi-squared test is a test to determine if there is an association between categorical variables. The test calculates the frequencies that would be expected if there were no association, and compares them to the observed numbers in each category in the table. If the observed numbers are significantly different to the expected numbers, this suggests there is an association. The greater the difference, the larger the chi-squared value. It then gives a P value based on the chi squared distribution formula with n degree of freedom where n is given by (number of rows -1) x (number of columns-1).

The test requires large sample size and less than 20% of the expected frequencies to be less than 5 and none less than 1. If that assumption does not hold, Fisher's exact test should be used. The test is also only valid if actual numbers are applied to the various categories and not proportions. The chi-squared test was therefore used to compare categorical variables except when the above assumptions were violated and a Fisher's exact test was used.

2.4 Cox regression

Cox regression, also known as proportional hazards regression, is commonly used to analyse survival time data in medical research. It also allows assessment of the effects of various predictor variables on the time-to-event outcomes. The predictor variables can be continuous, binary, or categorical data. A regression coefficient is given to represent the relationship between each predictor variable and the time-to-event outcome, after adjusting for all other variables in the model.

2.5 Kaplan-Meier curves

Kaplan-Meier curves display probabilities of survival over length of time on a graph. The x-axis is the length of survival time, and the y-axis is the cumulative probability of survival. The curve is stepped due to the occurrence of an event e.g. death.

2.6 Logrank test

Survival curves which consist of two groups or more on one graph require a statistical method that will compare the entire curve for each category. This can be done with the logrank test by utilising all the survival data from the entire curve. It is only a significance test giving a P value but not mortality estimate.

2.7 Statistical software

Analyses were performed using SPSS version 22 unless otherwise stated.

2.8 Statistical significance

P value of less than 0.05 is considered statistically significant unless specified otherwise.

Chapter 3

Clinical characteristics and outcomes of young and very young adults with heart failure: the CHARM programme.

3.1 Introduction

Because HF predominantly affects the elderly, most reports have appropriately focused on older patients.(144-146) However, HF also afflicts younger individuals, although little is known about the characteristics of these patients and their outcomes. Existing studies have largely defined "younger" as age less than 65 or 60 years, probably because most studies have small numbers of adults in the third to sixth decades of life.(85;94;101) As a result, there are few data describing the symptom burden, quality of life and hospitalisation and mortality rates in HF patients aged 20 to 60 years even though it is in these individuals where estimates of prognosis may be most keenly sought by patients and their families. Additionally and related to the latter, it is in younger patients that the most invasive and expensive therapeutic interventions are most commonly considered.(147;148) Consequently, knowledge of the causes, characteristics and consequences of HF in young patients is clinically important. We therefore analysed the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity programme (CHARM) database to provide a comprehensive description of heart failure in younger patients, comparing these individuals with older participants.

The CHARM programme enrolled a broad spectrum of patients with chronic heart failure who were 18 years or older. Detailed information was collected on symptoms, signs, quality of life, treatment, precipitants of hospitalisation and non-fatal and fatal outcomes.

3.2 Methods

3.2.1 Study design

The rationale, design, and baseline characteristics of patients in the CHARM programme and the primary analyses have been published in detail elsewhere.(149-154) The study was designed to assess the role of candesartan in managing a wide spectrum of

patients with HF. From the outset, the investigators were determined to enrol a wide representative population of patients with symptomatic HF. Among the wide spectrum of patients with HF, the use of candesartan was assessed in three distinct, parallel and linked populations to assess its impact on cardiovascular mortality and HF hospitalisation. Each arm of the study had the statistical power to detect an impact on cardiovascular mortality and HF hospitalisations.

Patients with symptomatic HF (New York Heart Association [NYHA] class II-IV) for at least 4 weeks duration who were 18 years or older receiving standard therapy (beta-blockers, diuretics, digitalis and spironolactone) were enrolled into one of three parallel clinical trials according to left ventricular ejection fraction (LVEF) and angiotensin converting enzyme inhibitor (ACEI) treatment: LVEF ≤ 40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative); LVEF ≤ 40% receiving ACEI treatment (CHARM-Added), and LVEF > 40% (CHARM-Preserved). The overall CHARM programme was designed to have adequate statistical power to assess the impact of candesartan on reducing mortality in the overall population of all three parallel studies. Exclusion criteria included serum creatinine ≥ 265 μmol/L or more, serum potassium 5.5 mmol/L or more, known bilateral renal artery stenosis, symptomatic hypotension, women of child bearing age potentially not using adequate contraception, critical aortic and mitral stenosis, myocardial infarction, stroke, or open-heart surgery in the previous 4 weeks, use of angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2-year survival, and unwillingness to consent. All participating centers received approval from local ethnics committees and all patients gave written consent prior to enrolment.

Between March 1999 and March 2001, 7599 patients (3803 candesartan, 3796 placebo) were randomised to candesartan 4 or 8 mg once daily or matching placebo. The dosage was doubled every two weeks, as tolerated to a target dose of 32mg once daily, with recommended monitoring of blood pressure and serum potassium and creatinine. Visits were scheduled for every 4 months for a minimum duration of 2 years after the initial dose titration. The programme was concluded, as planned, 2 years after the final patient was randomised, with a median duration of follow-up of 37.7 months.

The present analysis groups patients into five age categories: 20-39 (n=120), 40-49 (n=538), 50-59 (n=1527), 60-69 (n=2395), and ≥70 years (n=3019). The investigator-reported primary aetiology of HF was systematically collected using case report form (CRF) which consisted of eight options (ischemic heart disease, idiopathic dilated cardiomyopathy, hypertension, valvular heart disease diabetes mellitus, alcohol-related, atrial fibrillation and others). Adherence to study drug was assessed at each follow up visit. At each visit investigators assessed adherence based on patient's report, investigators inspection of pill bottles and a table count in cases of uncertainty. The investigators were asked to make an estimate of compliance with study drug by selecting one of the pre-defined categories (>80%, 20-80%, and <20% adherence) on the CRF. We calculated adherence as ([the number of visit when pills were taken as prescribed >80% of the time divided by the number of visits actually made] x100).(155) Patients recruited at the 243 sites in the United States and Canada were prospectively asked to participate in the CHARM health-related quality of life (HRQL) study. Enrolled patients completed the Minnesota Living with Heart Failure (MLwHF) questionnaire at baseline. The questionnaire contains 21 disease specific items with a score for each item ranging from 0 to 5 and a summary score of 0 to 105 (higher score represents worse quality of life). Data regarding acute episodes of decompensation after randomization were prospectively collected by using a specifically designed endpoint form documenting evidence of worsening HF, precipitating or aggravating factors, and intravenous treatment.

3.2.2 Statistical analysis

Baseline characteristics are reported as means and standard deviations for continuous variables and proportions for categorical variables. Variables were compared across age categories using ANOVA for continuous variables and Chi-square or Fisher's exact test for categorical variables. A conservative significance level of $p<0.0001$ was adopted for the comparison of baseline characteristics given the retrospective nature of the study and the multiple comparisons made. All-cause mortality (the primary endpoint of the overall programme), the composite endpoint of cardiovascular death or HF hospitalisation (the primary outcome of the three component trials), and the secondary pre-specified

endpoints were analysed by age group. Kaplan-Meier survival curves were plotted by age category, and event free survival estimated at one, two and three years. Cox's proportional hazard models were used to estimate the hazard of younger age compared with the age group 60-69 year as the referent category, adjusted for the previously published predictors of mortality and morbidity specific to each endpoint in the CHARM trial.(156) These predictors were age, diabetes: insulin-treated, diabetes: other, ejection fraction (per 5% decrease below 45%), previous HF hospitalisation, cardiomegaly, diagnosis of chronic HF over 2 years ago, NYHA class III, NYHA class IV, and diastolic blood pressure for cardiovascular death or HF hospitalisation; and age, ejection fraction (per 5% decrease below 45%), diabetes: insulin-treated, diabetes: other, BMI (per 1 kg/m^2 decreased below 27.5), female, NYHA class III, NYHA IV, current smoker, and bundle branch block for all cause mortality. For the survival analyses and multivariable models a conventional level of significance was used ($p<0.05$) and results presented with 95% confidence intervals.

3.3 Results

3.3.1 Demography, aetiology, and ejection fraction

Baseline characteristics stratified by age are presented in Table 3.1. There were 120, 538, 1527, 2395, and 3019 in age groups 20-39, 40-49, 50-59, 60-69, and ≥70 years, respectively. Younger patients were less often of European origin (youngest vs. oldest: 73% vs. 95%, $p<0.0001$) but more often of Black ethnicity (18% vs. 2%, $p<0.0001$), had a higher body mass index (29.8 kg/m2 vs. 27.0 kg/m2, $p<0.0001$) and were more likely to be obese (body mass index ≥35kg/m^2: 23% vs. 6%, $p<0.0001$). All age groups were predominantly male with the proportion of females increasing with age especially in the oldest age group (71%, 77%, 76%, 71% and 61% male in age groups 20-39 years, 40-49 years, 50-59 years, 60-69 years and ≥70 years respectively, $p<0.0001$) (Figure 3.1).

In the youngest age group, the commonest investigator-reported aetiology of HF was idiopathic dilated cardiomyopathy (IDCM), followed by a presumed ischemic aetiology and hypertension. The proportion of patients with a presumed ischemic and

hypertensive aetiology increased progressively with age: ischemic from 15% to 66% and hypertensive from 5% to 15%, comparing youngest and oldest, respectively ($p<0.0001$). The relative proportion of patients with IDCM declined with age, from 62% in those age 20-39 years to 9% ≥70 years ($p<0.0001$). Alcohol-related HF was more common in the youngest than in the oldest age group (3% vs. 0%, $p<0.0001$).

The mean EF was lowest in the youngest age group and increased steadily with age (34%, 37%, 38%, 38% and 40% in age group 20-39 years, 40-49 years, 50-59 years, 60-69 years and ≥70 years respectively; $p<0.0001$). Across the same age bands the prevalence of heart failure with reduced ejection fraction (HF-REF) [LVEF≤40%] was greatest in young patients and declined with age (70%, 66%, 64%, 63% and 55% respectively; $p<0.0001$) (Table 3.1; Figure 3.2).

3.3.2 Comorbidities

Myocardial infarction, angina, stroke, hypertension, diabetes, atrial fibrillation, previous coronary revascularisation and a pacemaker were less common in younger patients and increased in prevalence with advancing age (all $p<0.0001$) (Table 3.1). The prevalence of a prior HF hospitalisation was similar in all age categories likely reflecting the inclusion criteria in CHARM Added (patients in NYHA class II required hospitalisation for a cardiac condition within the past 6 months) and CHARM Preserved (patients required prior hospitalisation for a cardiac condition at any time). The prevalence of smoking peaked in the age-group 40-49 years (30%) and declined thereafter (8% in the elderly).

Table 3.1. Baseline characteristics stratified by age

Age Groups	**20-39** n=120	**40-49** n=538	**50-59** n=1527	**60-69** n=2395	**≥70** n=3019	P value
Male	71	77	76	71	61	<0.0001
Ethnicity European	73	82	86	91	95	<0.0001
Ethnicity Black	18	10	6	4	2	<0.0001
Body mass index (kg/m^2)	29.8 (7.3)	30.7 (6.6)	29.6 (5.9)	28.4 (5.1)	27.0 (4.7)	<0.0001
Body mass index (kg/m^2)						
<22.5	13	7	8	10	16	<0.0001
22.5-24.9	13	10	12	17	21	
25.0-29.9	37	35	38	42	41	
30.0-34.9	15	27	26	22	17	
≥35.0	23	21	16	10	6	
HF-REF vs. HF-PEF						
Ejection fraction (%)	34 (14)	37 (14)	38 (14)	38 (15)	40 (15)	<0.0001
HF-REF [EF≤40%]	70	66	64	63	55	<0.0001
HF-PEF [EF>40%]	30	34	36	37	45	<0.0001
Primary aetiology (%)						
Ischemic heart disease.	15	45	58	65	66	<0.0001
Idiopathic dilated cardiomyopathy	62	35	24	17	9	<0.0001
Hypertension	5	12	11	12	15	<0.0001
Valvular Heart Disease	3	2	1	2	3	0.001
Alcohol-related	3	2	2	1	0	<0.0001
Atrial Fibrillation	1	1	2	2	3	<0.0001
Medical History (%)						
Prior HF hospitalisation	83	71	71	71	71	0.257
Myocardial infarction	16	43	51	55	55	<0.0001
Angina (present)	5	19	24	25	24	<0.0001
Stroke	3	6	6	9	11	<0.0001
Hypertension	26	48	52	56	58	<0.0001
Diabetes Mellitus	15	24	30	32	26	<0.0001
Atrial Fibrillation	13	13	19	26	36	<0.0001
CABG	4	14	21	27	25	<0.0001
PCI	8	19	20	17	14	<0.0001
Permanent pacemaker	3	4	5	7	12	<0.0001
Current smoker	26	30	23	15	8	<0.0001
Medications (%)						
ACE inhibitor	53	48	47	43	35	<0.0001
Beta-blocker	62	63	63	57	48	<0.0001
Spironolactone	20	19	15	17	17	0.097
Digitalis	64	46	43	43	42	<0.0001
Diuretics	80	77	78	82	87	<0.0001
Medications [EF≤40%] (%)						
ACE inhibitor	69	64	62	57	49	<0.0001
Beta-blocker	66	63	63	56	48	<0.0001
Spironolactone	27	24	19	21	19	0.073
Digitalis	71	58	54	53	50	<0.0001
Diuretics	82	85	85	88	91	<0.0001
Adherence measure (%)						
Adherence to study drug	80	87	89	90	88	0.001

ACE=angiotensin converting enzyme; CABG=coronary artery bypass grafting; HF=heart failure; PCI=percutaneous coronary intervention; PEF=preserved ejection fraction; REF=reduced ejection fraction; SD=standard deviation.

Values are given as mean (standard deviation) or as percentage (%)

Figure 3.1. Distribution by age and sex

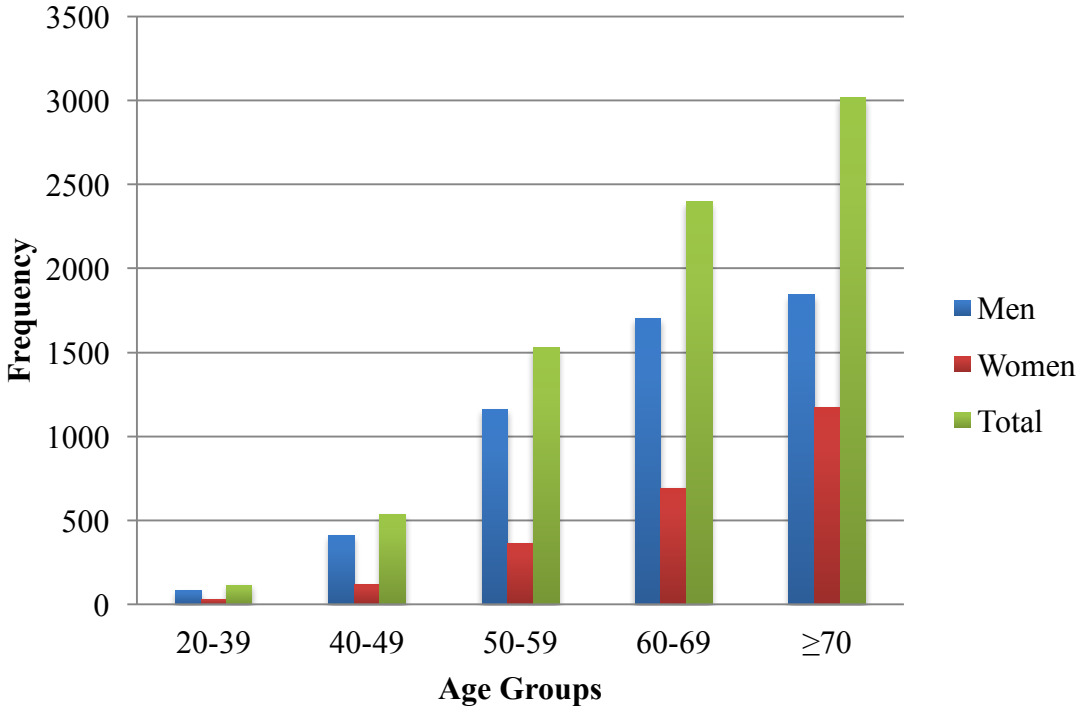
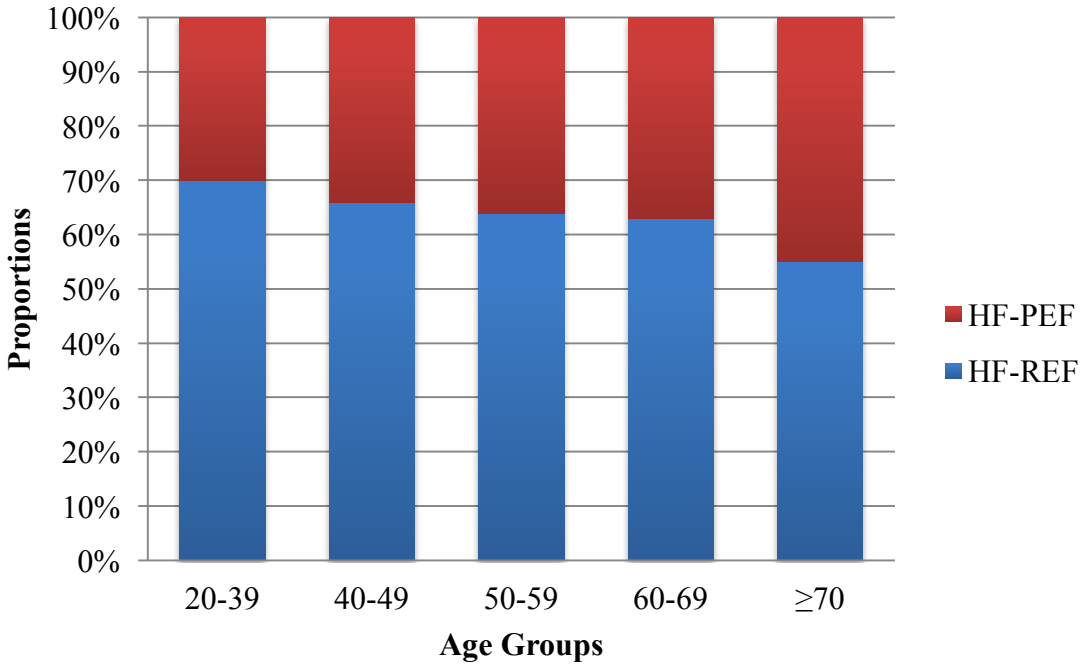


Figure 3.2. Histogram for HF-REF and HF-PEF by age



3.3.3 Symptoms and signs

The association between age and present symptoms (i.e. at randomisation) was inconsistent. (Table 3.2) In youngest patients, dyspnoea on level ground was less frequent (45% <40 years vs. 68% in ≥70 years, p<0.0001), yet PND was more prevalent (22% <40 years vs. 12% ≥70 years, p=0.001). The prevalence of rest dyspnoea, dyspnoea on climbing and orthopnoea was similar across all age categories. The youngest patients reported the worst quality of life scores, which improved with increasing age (mean MLwHF scores 52.6, 50.8, 47.1, 38.9 and 35.3 in age group 20-39, 40-49, 50-59, 60-69 and ≥70 years respectively; P<0.0001).

Past signs and present signs (i.e. reported prior to and at the time of randomisation) were consistent. The prevalence of JVP elevation was similar across age categories. A S3 gallop and hepatomegaly were more common in younger patients. Comparing youngest against oldest: S3 gallop 46% vs. 20% previously and 31% vs. 11% at randomisation; hepatomegaly 28% vs. 14% previously and 10% vs. 7% at randomisation (all p<0.0001). By contrast, signs of fluid extravasation (peripheral oedema and basilar pulmonary crackles) were less common in the younger patients. Systolic blood pressure was lowest and mean heart rate highest in younger patients (121 vs. 134 mmHg and 78 vs. 72 beats/min comparing <40 years against ≥70 years respectively, p<0.0001).

3.3.4 Investigations

A normal ECG was uncommon irrespective of age (9% vs. 8% youngest vs. oldest). (Table 3.3) Specific abnormalities were significantly less common in younger patients and increased with age, including atrial fibrillation or flutter (4% vs. 20%), bundle branch block (22% vs. 26%), paced rhythm (1% vs. 10%) and pathological Q waves (10% vs. 23%) (all p<0.0001). The exception was left ventricular hypertrophy, which occurred most frequently in the youngest age group (24% vs. 15%, p=0.032).

Radiological changes at randomisation were uncommon. Previous radiological abnormalities, however, exhibited a similar pattern to clinical signs (Table 3.3). Cardiomegaly was more common and fluid extravasation was less common in the young (interstitial pulmonary oedema 20% vs. 28%, bilateral effusions 6% vs. 19%, $p<0.0001$). The mean sodium, potassium, urea and creatinine were lower in younger patients, whereas the mean haemoglobin, white cell and platelet count were higher.

3.3.5 Baseline Medications

Compared with the oldest, the youngest patients were more likely to receive an ACE inhibitor (53% vs. 35%, $p<0.0001$), a beta-blocker (62% vs. 48%, $p<0.0001$), spironolactone (20% vs. 17%, $p=0.097$) and digoxin (64% vs. 42%, $p<0.0001$) (Table 3.1). Diuretic use was lowest in those aged 40 to 49 years and increased with age (80%, 77%, 78%, 82% and 87% in age group 20-39 years, 40-49 years, 50-59 years, 60-69 years and ≥70 years respectively; $p<0.0001$). These overall figures may be confounded by the higher proportion of HF-REF in young patients. However, similar therapeutic trends occurred comparing youngest with oldest in HF-REF alone: ACEI (69% vs. 49%, $p<0.0001$), beta-blockers (66% vs. 48%, $p<0.0001$), spironolactone (27% vs. 19%, $p=0.073$), and digoxin (71% vs. 50%, $p<0.0001$).

3.3.6 Adherence

Adherence to study drug was the lowest in the youngest age group (80%, 87%, 89%, 90% and 88% in age categories 20-39, 40-49, 50-59, 60-69 and ≥70 years respectively, $p=0.001$).

Table 3.2. Symptoms and signs stratified by age

Age Groups	**20-39** n=120	**40-49** n=538	**50-59** n=1527	**60-69** n=2395	**≥70** n=3019	P value
NYHA Class						
• II	53	49	48	46	42	<0.0001
• III	45	49	50	52	55	
• IV	2	2	2	3	3	
Minnesota score						
Mean (SD)	52.6 (27.6)	50.8 (24.9)	47.1 (24.3)	38.9 (23.9)	35.3 (21.6)	<0.0001
Median (IQR)	61.0 (28.0-73.0)	51.5 (32.5-72.0)	48.0 (28.0-65.0)	38.0 (18.0-58.0)	33.0 (18.0-50.0)	<0.0001
Past symptoms						
Dyspnoea at rest	62	53	48	47	49	0.009
Dyspnoea on flat	80	75	77	73	72	0.004
Dyspnoea on climbing	79	78	78	76	72	<0.0001
Orthopnoea	67	51	49	49	47	0.001
Paroxysmal nocturnal dyspnoea	63	46	43	40	38	<0.0001
Present symptoms						
Dyspnoea at rest	11	12	11	11	11	0.898
Dyspnoea on flat	45	59	60	63	68	<0.0001
Dyspnoea on climbing	93	90	92	91	91	0.790
Orthopnoea	26	22	20	19	21	0.086
Paroxysmal nocturnal dyspnoea	22	17	13	13	12	0.001
Heart rate & BP						
Heart rate	78 (12)	76 (14)	74 (14)	72 (13)	72 (13)	<0.0001
Systolic BP (mm Hg)	121 (17)	126 (18)	128 (18)	130 (19)	134 (19)	<0.0001
Diastolic BP (mm Hg)	78 (10)	79 (11)	78 (10)	77 (11)	75 (11)	<0.0001
Pulse pressure (mmHg)	43 (13)	46 (12)	50 (14)	54 (15)	59 (16)	<0.0001
Past signs						
Jugular venous pressure >6cm	36	27	28	25	26	0.038
Hepatomegaly	28	26	21	17	14	<0.0001
Peripheral oedema	53	49	50	51	54	0.039
Basilar pulmonary crackles	49	43	47	51	54	<0.0001
S3 gallop	46	33	27	23	20	<0.0001
Present signs						
Jugular venous pressure >6cm	10	9	9	9	10	0.719
Hepatomegaly	10	14	13	11	7	<0.0001
Peripheral oedema	19	21	24	26	30	<0.0001
Basilar pulmonary crackles	8	12	12	14	19	<0.0001
S3 gallop	31	15	12	12	11	<0.0001

BP=blood pressure; IQR=interquartile range; NYHA=New York Heart Association classification; SD=standard deviation.
Values are given as mean (standard deviation) or as percentage (%)

Table 3.3. Investigative findings stratified by age

Age Groups	**20-39** n=120	**40-49** n=538	**50-59** n=1527	**60-69** n=2395	**≥70** n=3019	P value
Electrocardiogram						
Normal	9	12	13	9	8	<0.0001
Atrial fib/flutter	4	7	11	14	20	<0.0001
Bundle branch block	22	17	22	25	26	<0.0001
Paced rhythm	1	3	3	5	10	<0.0001
Pathological Q waves	10	26	27	28	23	<0.0001
Left ventricular hypertrophy	24	17	16	16	15	0.032
Other abnormality	53	46	42	41	42	0.051
Chest X-Ray						
Interstitial pulmonary oedema	20	18	22	24	28	<0.0001
Bilateral effusion	6	7	11	13	19	<0.0001
Cardiomegaly	51	39	39	37	39	0.020
Ejection fraction						
Ejection fraction (%)	34 (14)	37 (14)	38 (14)	38 (15)	40 (15)	<0.0001
Biochemistry						
Sodium (mmol/l)	139.5 (3.7)	139.5 (3.4)	140.2 (2.8)	140.4 (2.9)	140.5 (3.1)	<0.0001
Potassium (mmol/l)	4.3 (0.5)	4.3 (0.5)	4.3 (0.4)	4.4 (0.5)	4.4 (0.4)	<0.0001
Urea (mg/dl)	14.7 (6.8)	17.2 (14.9)	16.6 (11.4)	18.6 (12.5)	19.8 (13.1)	<0.0001
Creatinine (mg/dl)	1.0 (0.3)	1.1 (1.6)	1.1 (0.4)	1.2 (0.4)	1.3 (0.7)	<0.0001
Haematological						
Haemoglobin (g/dl)	14.2 (1.5)	14.1 (1.6)	13.9 (1.5)	13.6 (1.7)	13.3 (1.6)	<0.0001
White cell count (10^3/mm^3)	7.6 (2.5)	7.9 (2.4)	7.5 (2.1)	7.3 (2.1)	7.2 (2.3)	0.001
Platelet count (10^3/mm^3)	223.2 (105.4)	192.8 (127.1)	171.7 (132.7)	150.7 (126.4)	130.8 (114.5)	<0.0001
Mean corpuscular volume (μm^3)	89.0 (5.9)	89.9 (5.3)	91.5 (5.3)	92.0 (6.1)	92.6 (6.0)	<0.0001

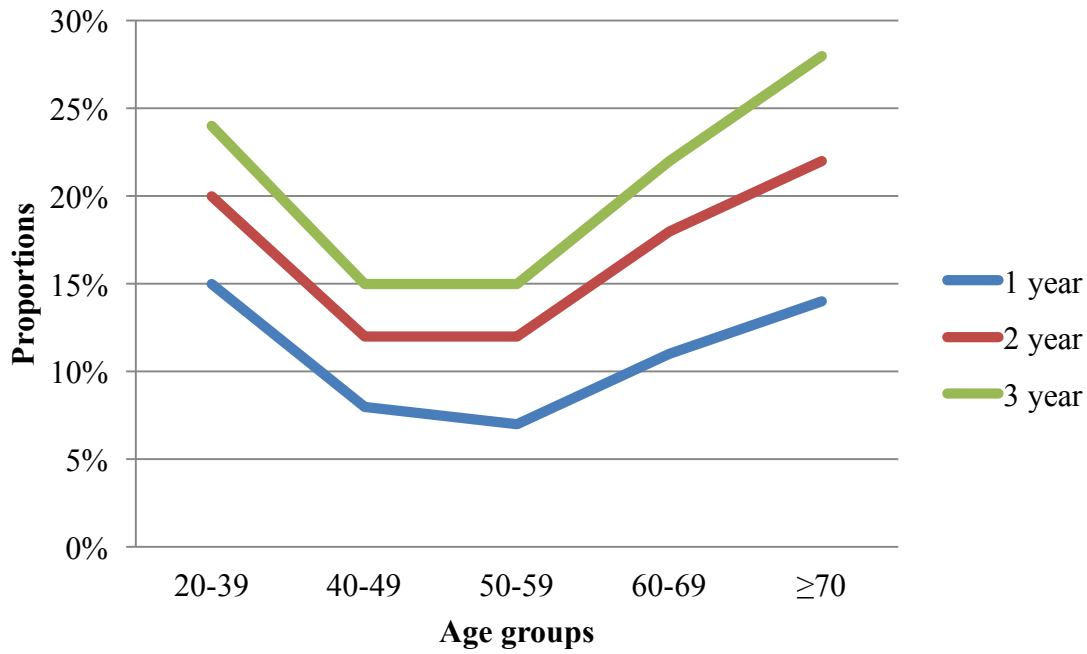
Values are given as mean (standard deviation) or as percentage (%)

3.3.7 Heart failure hospitalisation after randomisation

Patients aged 40 to 59 years had the lowest HF hospitalisation rate at 1, 2, and 3 years. (Figure 3.3) The youngest patients had similar HF hospitalisation rates to the oldest (20-39 years vs. ≥70 years: 1 year 15% vs. 14%; 2 years 20% vs. 22%; 3 years 24% vs. 28%). HF hospitalisation rates at 3 years were 24%, 15%, 15%, 22% and 28% in age categories 20-39, 40-49, 50-59, 60-69 and ≥70 years respectively. Younger patients were more likely to present with exertional dyspnoea, orthopnoea, nocturnal dyspnoea and fatigue at the time of HF hospitalisation (Table 3.4). As with clinical signs and past investigations, pulmonary oedema and radiological signs of HF were again less common in younger patients (youngest vs. oldest 24% vs. 35% and 28% vs. 53% respectively).

Lifestyle factors were often thought to have contributed to HF hospitalisation in younger patients, who were two to three times less likely to adhere to their medications and dietary restrictions (Table 3.4). Comparing youngest (20-39 years) with oldest (≥70 years) patients: medication non-adherence was 24% vs. 7% ($p=0.001$), dietary adherence 21% vs. 9% ($p=0.002$), reported alcohol excess 3% vs. 1% ($p<0.0001$). No significant difference was observed between age groups in acute treatment with intravenous diuretics, inotropes or vasodilators.

Figure 3.3. HF Hospitalisation by age groups



Age Groups	20-39 n=120	40-49 n=538	50-59 n=1527	60-69 n=2395	≥70 n=3019	P value
Hospitalisation rates [%(95% CI)]						
One year	15 (9-22)	8 (6-11)	7 (6-8)	11 (10-12)	14 (13-15)	<0.0001
Two year	20 (12-27)	12 (9-15)	12 (10-13)	18 (16-19)	22 (20-23)	<0.0001
Three year	24 (17-32)	15 (12-18)	15 (13-17)	22 (20-24)	28 (27-30)	<0.0001

Table 3.4. Clinical presentation, precipitating factors and treatment related to unplanned hospitalisation for heart failure occurring after randomisation

Age Groups	**20-39** n=120	**40-49** n=538	**50-59** n=1527	**60-69** n=2395	**≥70** n=3019	P value
Hospital stay						
Bed days [median (IQR)]	12 (6-33)	8 (4-21)	10 (4-21)	12 (6-25)	11 (5-21)	0.007
Clinical presentation						
Increasing dyspnoea on exertion	93	92	85	86	82	0.016
Orthopnoea	62	52	58	48	48	0.018
Nocturnal dyspnoea	48	48	42	36	36	0.051
Increasing peripheral oedema	41	51	52	46	45	0.052
Increasing fatigue or decreasing exercise tolerance	62	66	60	54	51	0.005
Renal hypoperfusion	7	11	18	20	20	0.051
Clinical pulmonary oedema	24	19	32	35	35	0.022
Radiological sign of heart failure	28	43	46	48	53	0.005
Precipitating factors						
Non-adherence with cardiac medications	24	13	15	7	7	0.001
Excessive salt intake/ dietary non-adherence	21	24	17	12	9	0.002
Alcohol excess	3	4	4	1	1	<0.0001
Inappropriate decrease of anti-failure therapy	7	5	3	6	6	0.055
Cardiac arrhythmias	17	22	26	29	28	0.002
Acute myocardial ischaemia	3	1	3	5	8	0.014
Intravenous treatment						
Diuretic	93	94	92	90	92	0.085
Inotropic agent	24	20	17	22	17	0.042
Vasodilator	10	15	13	17	17	0.072

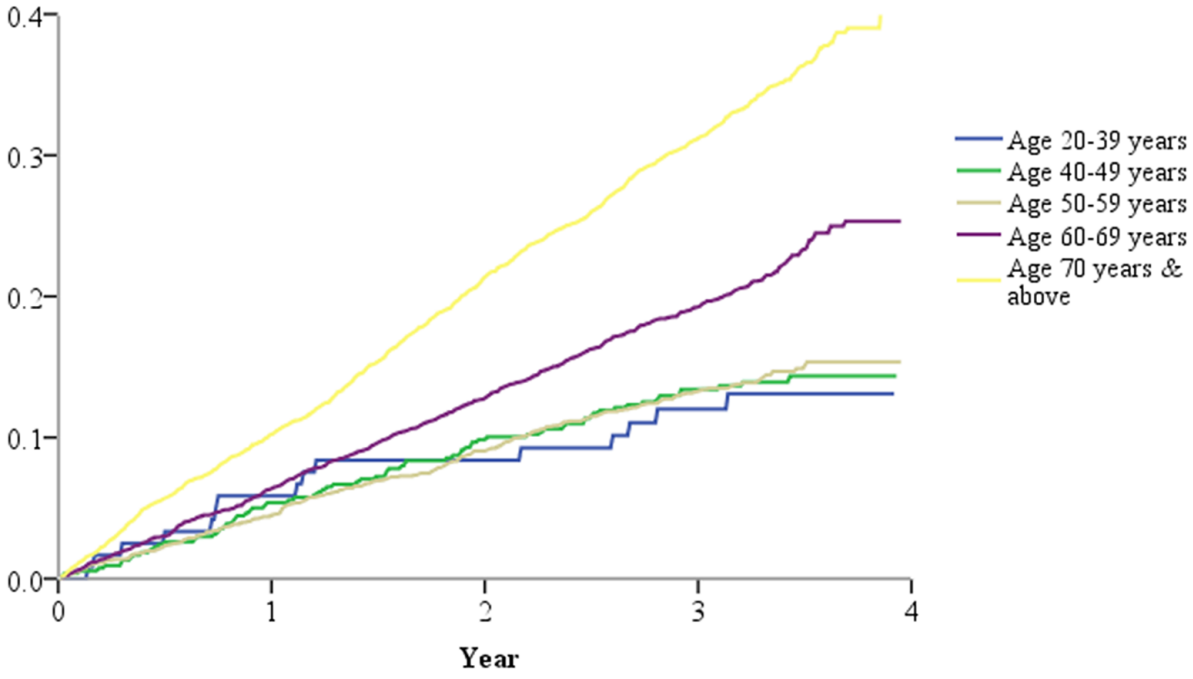
CI=confidence interval; IQR=interquartile range.
Values are given as median (IQR) or as percentage (%).

3.3.8 Mortality and cardiovascular outcomes

Crude mortality for any cause at 3 years was lowest in the youngest age group and increased with age, although only markedly above 60 years (12% < 40 years, 13% 40-49 years, 13% 50-59 years, 19% 60-69 years, and 31% ≥70 years, p<0.0001) (Figure 3.4). This remained the case after adjusting for previously published predictors of mortality and morbidity (Figure 3.5). The inclusion of the ethnicity (European origin, Black, South Asian, Arab/Middle East, Oriental, Malay or other) and geographical regions of patients into the model made little difference to the adjusted outcomes and there was no interaction between age and ethnicity (p=0.71) or age and regions (p=0.28). The respective hazard ratios for age group <40, 40-49 and 50-59 years referenced to 60-69 years were 0.60 (95% CI 0.36-1.00) [p=0.049], 0.63 (95% CI 0.50-0.81) [p<0.0001] and 0.64 (95% CI 0.54-0.75) [p<0.0001] for all-cause mortality; for cardiovascular death 0.71 (95% CI 0.42-1.18) [p=0.186], 0.78 (95% CI 0.60-1.00) [p=0.054] and 0.70 (95% CI 0.59-0.84) [p<0.0001].

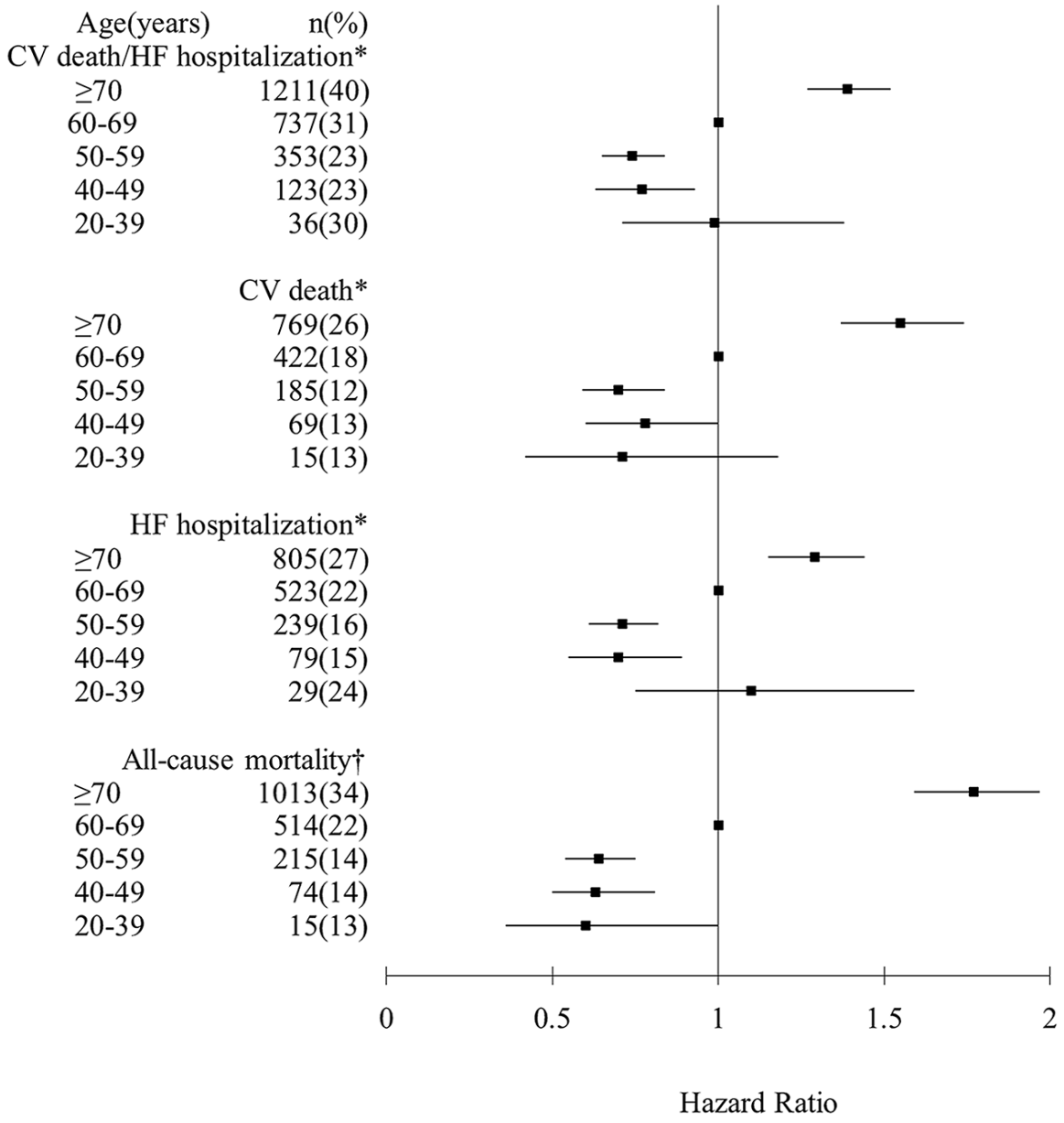
The association between age and cardiovascular death or HF hospitalisation was non-linear. The youngest age group had similar risk of cardiovascular death or HF hospitalisation to the referent age group 60-69 years (HR 0.99 [95% CI 0.71-1.38], p=0.930). This was driven by the aforementioned higher risk of HF hospitalisation in the youngest age group (Figure 3.5). However, the absolute number of events in this group was small resulting in wide confidence intervals.

Figure 3.4. Kaplan-Meier mortality curves in age categories for all-cause mortality



	Cumulative mortality rate [%(95% CI)]		
	1-year	2-year	3-year
20-39 years	6 (2-10)	8 (3-13)	12 (6-18)
40-49 years	5 (4-7)	10 (7-12)	13 (11-16)
50-59 years	5 (4-6)	9 (8-11)	13 (12-15)
60-69 years	6 (5-7)	13 (11-14)	19 (18-21)
≥ 70 years	10 (9-11)	21 (20-23)	31 (30-33)

Figure 3.5. Adjusted hazard ratios for the primary outcome, secondary components and all-cause mortality by age categories, with 60-69 years as the reference group



CI=confidence interval; CV=cardiovascular; HF=heart failure.
*Adjusted for age, diabetes: insulin-treated, diabetes: other, ejection fraction (per 5% decrease below 45%), previous HF hospitalisation, cardiomegaly, diagnosis of chronic HF over 2 years ago, NYHA class III, NYHA class IV, and diastolic blood pressure.
†Adjusted for age, ejection fraction (per 5% decrease below 45%), diabetes: insulin-treated, diabetes: other, BMI (per 1 kg/m^2 decreased below 27.5), female, NYHA class III, NYHA IV, current smoker, and bundle branch block.

3.4 Discussion

With nearly 2,200 patients younger than 60 years, I have demonstrated some striking differences from older patients with HF. Younger patients with HF have different demographics, aetiology, co-morbidity, symptoms, signs, quality of life, investigative findings, treatment adherence, potential precipitants of decompensation and non-fatal and fatal outcomes. I am not aware of any similarly comprehensive study of younger patients with heart failure.

3.4.1 Characteristics

That more younger patients were black is consistent with epidemiological studies in the USA showing that African-Americans have a higher risk of developing heart failure than whites and do so at a younger age.(157) Similarly, a higher proportion of younger patients had an investigator-reported aetiology of IDCM (and a smaller proportion an ischemic aetiology), is consistent with the occurrence of symptomatic coronary heart disease later in life.(145;158) Previous clinical trials(14;82;88;89) and survey/registries(94;95;159) reported a higher proportion of IDCM in younger patients with HF. Interpretation of this apparent association between age and aetiology requires consideration of both numerator and denominator. In fact, the incidence and prevalence of IDCM increase steadily with age in the general population.(160;161) However, the incidence and prevalence of the two commonest alternative aetiologies (ischaemia and hypertension) rise even more rapidly with age, thus diminishing the relative frequency of DCM in patients with an established diagnosis of HF.

The lower prevalence of all co-morbidities, including diabetes mellitus, hypertension and stroke, likewise reflects the conditions occurring beyond middle-age.(93;94;145) As comorbidities (along with age) are among the most powerful predictors of prognosis, these findings are central to the much better survival of younger patients (see below).(101;162) Atrial fibrillation was also significantly less common in younger patients whether identified by medical history at baseline (13% versus 36% youngest versus oldest)

or on the baseline ECG (4% versus 20%). This suggests that atrial fibrillation may be an age-related comorbidity in heart failure rather than just a consequence of heart failure, especially as severity of heart failure (associated with the prevalence of AF) did not differ greatly across age groups.(69;93;94) Interestingly, the youngest age group combined the lowest prevalence of AF with highest prescribing rate of digoxin. Trial enrolment from 1999 closely followed publication of the Digitalis Investigation Group trial. Most likely, the aforementioned higher hospitalisation rates, non-ischemic aetiology, radiologic cardiomegaly and worse LVEF and quality of life prompted physicians to prescribe digoxin more frequently in younger patients.(163)

3.4.2 Symptoms and signs

Although younger patients had a slightly but significantly more favourable NYHA class profile (i.e. a greater proportion NYHA class II/smaller proportion NYHA class III/IV) than older participants, they had strikingly worse HRQL, as assessed by the MLwHF. This disconnects between NYHA class and MLwHF score is of interest and may in part reflect the difference between a physician-based assessment (NYHA class) and a patient-reported one (MLwHF). That younger patients report worse HRQL has been reported before and likely reflects the greater impact of heart failure symptoms and functional limitation in an age group that is more active (or desires to be more active) in meeting the demands of employment and family/social commitments.(90;117) Of interest, in connection with this, younger patients reported more heart-failure related symptoms in the past. Although this finding was not so clear for the current symptoms reported by patients at baseline, the difference in symptoms between younger and older patients was also noted during episodes of decompensation after randomization.

The pattern of HF signs also differed strikingly between younger and older subjects. In particular, younger patients seemed less likely to develop peripheral or pulmonary oedema. Evidence for this was seen in previous and current signs and in chest radiographic findings (pulmonary oedema and effusions less frequent) collected at baseline; the same differences were noted during episodes of decompensation reported after randomization. Intriguingly, less peripheral oedema was noted in younger subjects

despite a higher prevalence of an elevated JVP and hepatomegaly in these patients (compared with older ones) and less pulmonary oedema despite a lower LVEF and higher prevalence of a third heart sound. This suggests, perhaps, that peripheral and pulmonary endothelial integrity diminishes with age, leading to increasing capillary "leakiness". These findings also have potential clinical importance for the recognition of heart failure in younger individuals. Heart failure is unlikely to be high on the list of differential diagnoses in young subjects with breathlessness and if the most easily detectable and commonly recognized signs of heart failure (i.e. peripheral and pulmonary oedema) are less common in these individuals, the diagnosis may be delayed.

Other clinical and investigative findings in younger subjects of relevance to patient management were lower systolic blood pressure, better renal function and less frequent bundle branch block.

3.4.3 HF hospitalisations

One particularly unique aspect of the current study was the prospective collection of information about acute episodes of decompensation after randomization using a specifically designed endpoint form. Non-adherence with medication and life-style measures was reported as a possible contributor to heart failure worsening significantly more frequently in younger than in older subjects. Previous studies reported conflicting results, some supporting ours,(164;165) and others not.(111) The recent Get With The Guidelines-Heart Failure (GWTG-HF) program, which prospectively included 95127 patients hospitalised with acute HF, reported patients with non-adherence (less compliant with medication or dietary restriction or both) were younger (non-adherence vs. adherence 64 years vs. 74 years, $p<0.0001$).(164) After multivariate analysis, younger age was independently associated with non-adherence (Odds ratio for the outcome of non-adherence in younger age [per each year decrease]: 1.022 [95% CI: 1.019-1.026], $p<0.001$). Younger patients with heart failure may therefore merit particular attention in terms of education and other interventions to improve adherence. In keeping with their lower prevalence of comorbidity, younger patients were less likely to have decompensation attributed to myocardial ischemia or arrhythmias.

3.4.4 Outcomes

Finally, I demonstrated a possible important divergence between fatal and non-fatal outcomes in younger versus older patients. As expected, younger patients had a significantly lower mortality rate than older subjects. However, there was a suggestion that the youngest patients (aged 20-39 years) may have relatively high hospitalisation rates, more in keeping with those aged ≥ 60 years than those aged 40 – 59 years. This divergence was not unexpected given the lower mortality in the youngest patients which increased the period at risk of further hospital admission. Coupled with non-adherence to study drug, cardiac medications, dietary restriction and alcohol excess, this may explain the disconnect of higher HF hospitalisation alongside lower mortality in the youngest compared to older patients. The modest number of patients in the youngest age group with a wide confidence interval reduces certainty in this finding. However, the longer duration of admission experienced by these patients is consistent with the possibility that they had more severe heart failure, as was the greater use of digoxin (despite less atrial fibrillation) and spironolactone in this age group. Of additional interest, mortality rates appeared to be relatively flat across the age range 20-59 years, only increasing notably in subjected aged 60-69 years and rising again substantially in those aged 70 years or above; this three-step pattern was as apparent for death from cardiovascular causes only and persisted after adjustment for differences in known prognostic variables that differed in frequency across the age groups.

3.5 Limitations

A number of limitations merit consideration. The number of patients in the youngest age group was small. This resulted in wider confidence intervals and a greater degree of uncertainty when interpreting results. Symptoms are susceptible to recall bias. The aetiology of HF and ECG interpretation were reported by individual site investigators rather than by a core laboratory with standardized definitions. Systematic investigation of the aetiology of HF was not mandatory in the study protocol. Serum albumin was not available for the entire cohort. The study excluded the sickest young patients on heart transplant waiting list. This might have altered the mortality and morbidity outcomes.

Conversely the inclusion and exclusion criteria of a trial tend to have a greater impact on the older participants who have more comorbidities (as we have found here again in CHARM). Therefore, older participants are likely to be healthier and consequently I believe that the inclusion and exclusion criteria are likely to have biased the true difference between young and old towards the null, underestimating the difference.

3.6 Conclusion

In summary, comparing with older patients, younger patients with HF have a markedly different clinical characteristics, including a different pattern of symptoms and signs which could lead to delayed diagnosis, a poorer health related quality of life, more hospitalisations attributed to non-adherence but lower mortality, with relatively low rates of death until the age of 60 year.

Chapter 4

Heart failure in younger patients: the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) database.

4.1 Introduction

Although the overall prevalence of heart failure (HF) in the general adult population is 1–2%,(166;167) the majority of those affected are elderly.(51) Prior studies on the epidemiology and prognosis of HF have focussed on older individuals.(12;24;168;169) There is limited information on the causes and consequences of HF in younger patients (<60 years) especially those aged <40 years.(93;94) This is primarily because no single epidemiological study, registry or clinical trial has included sufficient numbers of such individuals to draw robust conclusions. Yet it is often in these younger patients that the most searching questions about aetiology and prognosis are asked.

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) has collated individual patient data from 31 studies (24 observational studies including the Euro Heart Failure Survey(170) and 7 randomised controlled trials of either pharmacotherapy or management interventions). The data provides an opportunity to address these deficiencies in our understanding of HF in younger patients.(171)

4.2 Methods

4.2.1 Study design

The details of the rationale, methods, inclusion and exclusion criteria and results of the meta-analysis have been published previously.(171) A comprehensive literature search of Embase, Medline and PubMed was undertaken for observational studies and randomised controlled trials published to the end of 2008, using the following keywords: heart failure, left ventricle, prognosis, outcome, and preserved. The reference lists of each article and conference abstracts were scrutinised and investigators and authors contacted. Abstracts, unpublished studies and articles published in languages other than English were not excluded. The inclusion criteria were that each study had a prospective study design, that left ventricular ejection fraction (LVEF) was not an inclusion criterion and all-cause mortality was reported. Each individual study was approved by the local ethics committees

and the meta-analysis was approved by The University of Auckland Human Subjects Ethics Committee.

Principal investigators from 56 potentially suitable studies were invited to participate in the meta-analysis, from which 31 investigators contributed individual patient data. These data included demographics (age, sex, and ethnicity), medical history (myocardial infarction, coronary revascularisation, diabetes, hypertension, atrial fibrillation, stroke, lung disease, peripheral artery disease, and smoking), aetiology (defined by individual studies; idiopathic included those labelled as idiopathic or dilated cardiomyopathy), medical treatment (angiotensin converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], beta-blocker, diuretics, and aldosterone antagonist), symptom status (New York Heart Association [NYHA] functional class, dyspnoea, paroxysmal nocturnal dyspnoea, and oedema), clinical variables (heart rate, blood pressure, and pulmonary rales), laboratory variables (serum sodium, creatinine, and EF), and outcomes (deaths and follow up duration). The results from the MAGGIC meta-analysis demonstrated that patients with HF with preserved LVEF (HF-PEF) have lower risk of death from any cause than patients with reduced LVEF (HF-REF).(171) In the present study patients were stratified into 6 age categories (<40, 40-49, 50-59, 60-69, 70-79, and ≥80 years) and report their clinical characteristics and outcomes.

4.2.2 Statistical analysis

The current analyses included all subjects in the MAGGIC dataset for whom LVEF category (HF-PEF or HF-REF) was known. Baseline characteristics are presented as means and standard deviations for continuous variables and proportions for categorical variables. Variables were compared across age categories using ANOVA for continuous variables and Chi-square for categorical variables. For all analyses the primary outcome was rate of death from any cause at 3 years from hospital discharge or baseline study visit. Mortality estimates, stratified by age and sex, at 1, 2 and 3 years and deaths per 1000 patient-years were calculated. Baseline characteristics, mortality rates, and survival curves were stratified by ejection fraction as HF-REF and HF-PEF. Cox's proportional hazard models were used to estimate the hazard of younger age compared with the age group 50-59 years as the referent category. All models were adjusted for sex, aetiology (ischaemic vs. non-ischaemic), LVEF (reduced [defined as LVEF <50%] vs. preserved), history of hypertension, diabetes, and atrial fibrillation, and stratified by individual study. Included

variables were selected based on clinical relevance and where data were available for >90% of the patients in the MAGGIC dataset. Data regarding NYHA functional class and medications were less complete, so models were re-analysed with these variables included as a sensitivity analysis. The presence of an age-sex interaction was assessed in the main model. Mortality curves for each age category were created using adjusted models that were not stratified by individual study. Analyses were performed using SAS version 9.2.

4.3 Results

4.3.1 Demography

Thirty-one studies contributed data on 41,926 patients whose baseline characteristics are presented in Table 4.1. The relative proportion of women increased with age (29% <40 years, 22% 40-49 years, 23% 50-59 years, 27% 60-69 years, 38% 70-79 years, and 52% ≥80 years; p<0.0001).

4.3.2 Comorbidities

Younger patients had the lowest prevalence of comorbidities (<40 vs. ≥80 years: hypertension 22% vs. 43%, p<0.0001; MI 14% vs. 35%, p=0.019; AF 9% vs. 30%, p<0.0001; and diabetes 9% vs. 18%, p<0.0001) [Table 1]. The prevalence of comorbidities increased with age.

4.3.3 Aetiology

The aetiology of HF varied with age. Since the term 'idiopathic' may refer to dilated cardiomyopathy (typically inferring reduced ejection fraction), aetiology was examined separately in the overall population and those with HF-REF (Table 1). In both cohorts, the youngest age group had the highest proportion of 'idiopathic' cardiomyopathy, which declined sharply above 40 years of age (Overall 63% <40 years, 37% 40-49 years, 28% 50-59 years, 20% 60-69 years, 12% 70-79 years and 7% ≥80 years; p<0.001). This reflected converse parallel trends in the proportion of patients with ischaemic and hypertensive aetiology which both increased with age: aetiology presumed to be ischaemic increased from 16% of those aged <40 years to 68% ≥80 years (p<0.0001); hypertensive

from 5% <40 years to 17% ≥80 years (p=0.18). The proportion of HF attributed to alcohol was low in all age categories, ranging from 0% to 4%.

4.3.4 HF-REF and HF-PEF

Median EF was lowest in the youngest and progressively increased with age (31% <40 years, 33% 40-49 years, 33% 50-59 years, 34% 60-69 years, 37% 70-79 years and 42% ≥80 years; p<0.0001). The proportion of patients with HF-PEF (LVEF ≥50%) trebled from youngest to oldest age groups: 14% in < 40 years of age to 39% in those age ≥ 80 (p<0.0001) [Table 1].

4.3.5 Clinical status, blood pressure, heart rate, and treatment

Younger patients were predominantly in NYHA functional class I or II. The proportion of patients in NYHA functional class III and IV increased with age. Mean systolic blood pressure was lowest in the youngest age group (118±19 mmHg <40 years vs. 137±26 mmHg ≥80 years; p<0.0001). Younger patients were more likely to receive disease-modifying medical therapies, including an ACEI or ARB, a beta-blocker, and spironolactone. Younger patients were also more often treated with digoxin, despite their much lower prevalence of atrial fibrillation. Excluding the DIG trial from the analysis, similar patterns were observed. By contrast, younger patients were less likely to receive diuretics (70% <40 years vs. 85% ≥80 years; p<0.0001).

Table 4.1. Baseline characteristics for patients from the MAGGIC meta-analysis by age categories

Age (years)	<40	40-49	50-59	60-69	70-79	≥80	p value
N (31 studies)	876	2638	6894	12071	13368	6079	
Women (%)	29	22	23	27	38	52	<0.0001
• RCTs.	29	22	23	26	35	51	
• Observational studies.	29	22	22	29	40	53	
Medical history							
Hypertension (%)	22	37	41	44	46	43	<0.0001
MI (%)	14	38	46	50	47	35	0.019
Atrial fibrillation (%)	9	9	14	18	25	30	<0.0001
Diabetes (%)	9	18	24	27	25	18	<0.0001
Aetiology							
All patients							
Ischaemic	16	46	57	65	69	68	<0.0001
Hypertensive	5	10	9	10	13	17	0.180
Idiopathic	63	37	28	20	12	7	<0.0001
Alcoholic	3	3	2	1	1	0	<0.0001
Atrial fibrillation	9	4	4	4	5	8	<0.0001
Patients with HFREF							
Ischaemic	17	46	58	68	73	76	<0.0001
Hypertensive	4	8	8	8	9	10	0.170
Idiopathic	65	38	29	21	14	9	<0.0001
Alcoholic	3	4	2	1	1	0	<0.0001
Atrial fibrillation	11	4	3	2	3	5	<0.0001
Clinical status							
NYHA class(%) (I/II/III/IV)	21/50/25/4	14/50/31/5	11/50/34/5	10/49/35/6	9/45/38/9	9/40/37/14	<0.0001
Heart rate (b.p.m) [SD]	81 (17)	80 (16)	79 (17)	78 (17)	79 (19)	82 (22)	0.820
SBP (mmHg) [SD]	118 (19)	124 (20)	126 (21)	130 (22)	134 (23)	137 (26)	<0.0001
DBP (mmHg) [SD]	76 (12)	79 (13)	78 (12)	77 (12)	76 (13)	76 (14)	<0.0001
Medication							
All patients							
ACEI or ARB	80	77	74	71	65	53	<0.0001
Beta-blocker	45	47	47	39	34	26	<0.0001
Spironolactone	26	26	23	22	21	19	<0.0001
Digoxin	49	47	44	44	42	41	<0.0001
Diuretic	70	75	78	81	84	85	<0.0001
Patients with HFREF							
ACEI or ARB	84	82	80	77	73	63	<0.0001
Beta-blocker	47	47	48	40	39	27	<0.0001
Spironolactone	28	28	25	24	23	22	<0.0001
Digoxin	52	51	48	48	45	43	<0.0001
Diuretic	71	77	79	72	85	87	<0.0001
Ejection Fraction							
median EF (%), IQR	31 (23, 42)	33 (24, 32)	33 (24, 43)	34 (26, 46)	37(27, 51)	42 (30, 58)	<0.0001
HF-PEF (%)	14	15	17	21	38	39	<0.0001

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; b.p.m=beats per minute; DBP=diastolic blood pressure; HF-PEF=heart failure with preserved ejection fraction (LVEF >50%); HF-REF: heart failure with reduced ejection fraction; IQR=inter-quartile range; LVEF=left ventricular ejection fraction; MI=myocardial infarction, NYHA=New York Heart Association functional class; SBP=systolic blood pressure; SD=standard deviation.

4.3.6 Mortality

During 3 years follow up 10,747 patients died. Deaths per 1000 patient-years increased with age from 64 (95% CI 53,78) in the youngest to 276 (95% CI 266,287) in the oldest age group. Likewise, the probability of death was lowest in the youngest age group and increased with age (Table 4.2). The estimated 3 year cumulative mortality was 16.5% < 40 years, 16.2% 40-49 years, 18.2% 50-59 years, 26.2% 60-69 years, 37.5% 70-79 years and 57.2% ≥ 80 years (Table 4.2). There was no significant age-sex interaction for all-cause mortality. The mortality rates in younger patients with HF-PEF were half that of patients with HF-REF (deaths per 1000 patient-years: HF-PEF vs. HF-REF: 19.3 vs. 70.9 in < 40 years, 31.7 vs. 68.9 in 40-49 years, and 42.1 vs. 80.0 in 50-59 years) (Table 4.3). The deaths per 1000 patient-years were similar for patients in the RCTs compared to those in the observational studies.

After adjusting for sex, ischaemic aetiology, diabetes, hypertension and atrial fibrillation, mortality remained lowest in the youngest patients (< 60 years) in patients with both HF-REF and HF-PEF (Figure 4.1A and 4.1B). The hazard ratios for all-cause mortality increased with increasing age, being lowest in those aged <60 years (Figure 4.2). The hazard ratios for the 3 youngest age groups (<40 years, 40-49 years and 50-59 years) did not differ significantly. A sensitivity analysis incorporating NYHA class, ACEI, ARB and beta-blocker use did not alter the effect of age on outcome.

Table 4.2. Mortality probability estimates (%) stratified by sex and age categories at 1, 2 and 3 years, adjusted for ischemic aetiology, diabetes, hypertension, EF group (HF-REF vs. HF-PEF), and atrial fibrillation.

Age groups		<40	40-49	50-59	60-69	70-79	≥80
One year	all patients	6.7	6.6	7.5	11.2	16.7	28.2
	male	7.3	6.9	7.7	11.5	17.3	28.9
	female	5.4	5.9	7.3	10.8	15.8	26.8
Two years	all patients	11.7	11.5	13.0	19.1	27.8	44.5
	male	12.9	12.2	13.6	19.9	29.3	46.4
	female	9.1	9.8	12.1	17.5	25.2	41.1
Three years	all patients	16.5	16.2	18.2	26.2	37.5	57.2
	male	18.1	17.1	19.1	27.6	39.5	59.5
	female	12.6	13.7	16.7	24.0	33.8	52.9

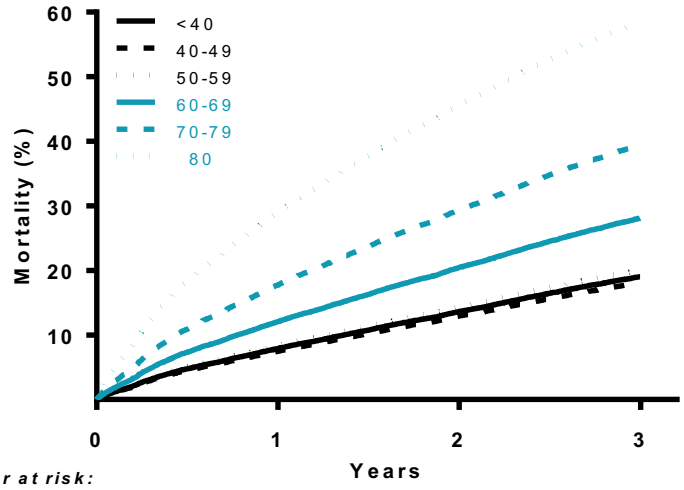
Age-sex interaction p=0.78

Table 4.3. Deaths per 1000 patient years stratified by age and ejection fraction

Age (years)	<40	40-49	50-59	60-69	70-79	≥80
All Studies						
Whole group	64.2 (52.6, 77.6)	60.1 (53.7, 67.2)	73.2 (68.8, 77.8)	109.5 (105.3, 109.7)	161.1 (156.2, 166.2)	276.0 (265.7, 286.6)
HF-PEF	19.3 (0.61, 46.5)	31.7 (20.8, 46.5)	42.1 (34.6, 50.8)	78.5 (71.2, 86.4)	125.9 (118.0, 134.3)	239.9 (225.1, 255.4)
HR-REF	70.9 (57.9, 86.1)	68.9 (61.6, 77.0)	80.0 (74.9, 85.3)	118.0 (113.0, 123.0)	176.0 (170.0, 182.0)	301.0 (287.0, 316.0)
Observational studies						
Whole group	68.7 (51.4, 90.1)	69.6 (57.8, 80.1)	77.3 (69.7, 89.6)	113.8 (106.5, 121.6)	174.4 (166.2, 182.8)	289.5 (275.3, 304.3)
HF-PEF	31.5 (1.0,71.9)	48.6 (26.0, 81.7)	59.9 (45.0, 76.0)	88.5 (76.3, 102.2)	143.2 (130.6, 156.7)	255.4 (235.3, 276.7)
HR-REF	76.8 (56.7, 102.0)	73.3 (60.3, 88.4)	81.9 (73.2, 91.5)	122.9 (114.0, 132.4)	189.9 (179.5, 200.7)	315.7 (296.0, 336.3)
RCTs only						
Whole group	60.6 (45.8, 78.6)	60.6 (52.9, 69.2)	71.1 (65.8, 76.7)	107.4 (102.4, 112.5)	140.8 (135.0, 146.9)	259.9 (245.3, 275.3)
HF-PEF	-	23.7 (12.8, 40.2)	31.6 (23.6, 41.5)	72.2 (63.3, 81.9)	112.3 (102.3, 122.9)	219.2 (197.9, 242.3)
HF-REF	66.6 (50.4, 86.5)	66.9 (58.14, 76.6)	79.0 (72.9, 85.5)	116.1 (110.3, 122.0)	167.5 (160.1, 175.3)	285.6 (266.0, 306.2)
P value (observational vs RCTs)						
Whole Group	0.530	0.230	0.200	0.160	<0.0001	0.006
HF-PEF	-	0.089	0.002	0.041	0.0002	0.002
HF-REF	0.490	0.440	0.600	0.210	<0.0001	0.039

Figure 4.1 Mortality curve adjusted for sex, ischemic aetiology, diabetes, hypertension, and atrial fibrillation stratified by age for A) HF-REF and B) HF-PEF.

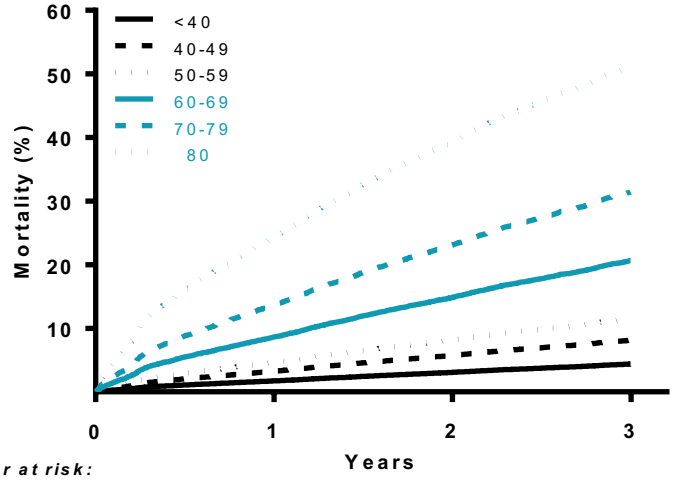
A. HF-REF



Number at risk:

<40	718	532	394	298
40-49	2130	1670	1310	1026
50-59	5440	4120	3403	2636
60-69	9099	6860	5531	4136
70-79	9246	6507	5094	3617
80	3562	2090	1531	1050

B. HF-PEF

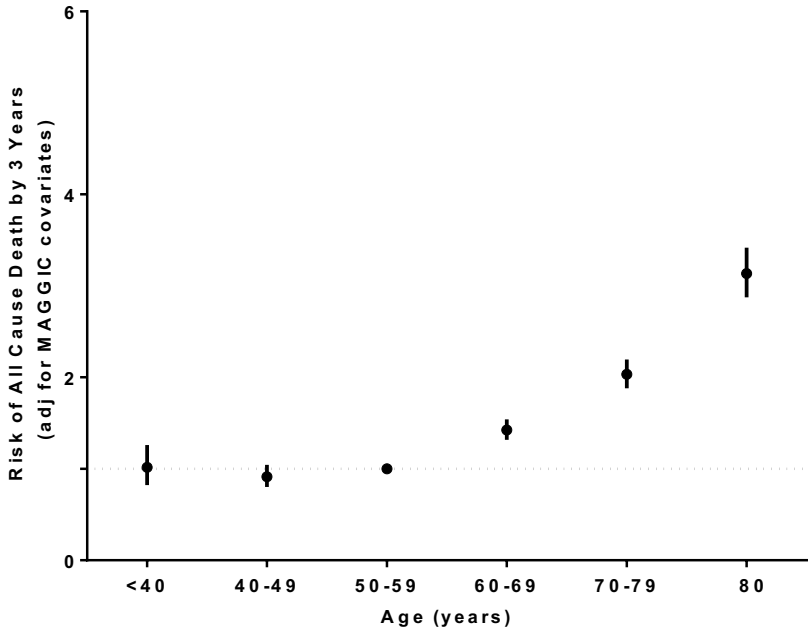


Number at risk:

<40	113	76	59	47
40-49	367	262	236	175
50-59	1141	838	786	608
60-69	2451	1826	1619	1251
70-79	3629	2554	2202	1678
80	2293	1444	1112	793

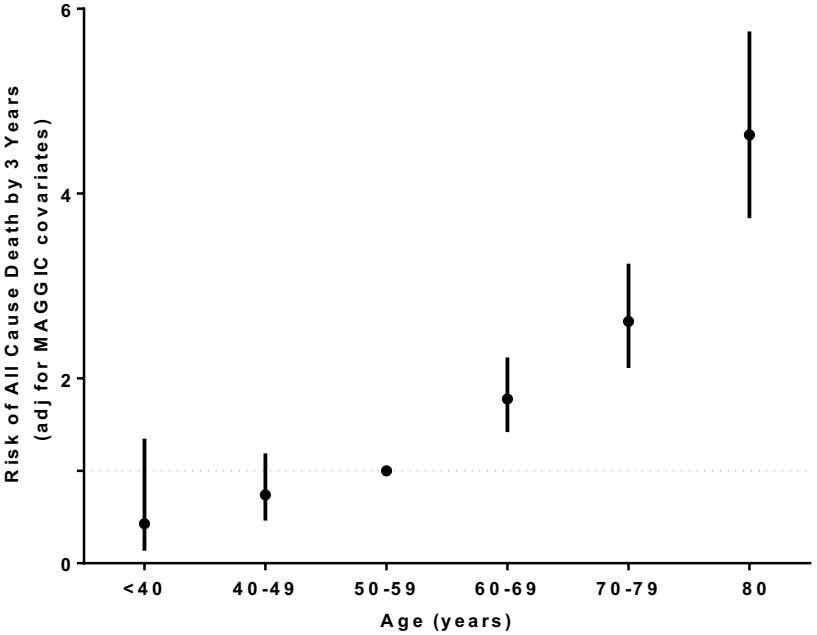
Figure 4.2 Adjusted hazard ratios for all-cause mortality by age categories, with 50-59 years as the reference group

A.HF-REF



Number of deaths	98	307	910	2197	3091	1722
Number in group	718	2130	5440	9099	9246	3562

B.HF-PEF



Number of deaths	4	24	104	410	920	960
Number in group	113	367	1141	2451	3629	2293

4.4 Discussion

Young patients with HF have different demographics, aetiology, clinical characteristics and survival compared to older age groups.

4.4.1 Aetiology and demographics

Presumed "idiopathic" dilated cardiomyopathy is relatively more common in young patients. The relative frequency of DCM is ten times higher in the youngest (< 40 years) compared to the oldest (63% v 7%). These proportions are comparable to previous clinical trials(82;87;90) and registries(93-96), which reported a higher prevalence of presumed non-ischaemic (25-58%) or idiopathic dilated aetiology (6-40%) in those aged <50-65 years, compared to 2-36% in those aged ≥70-80 years. In both the current analysis and previous reports, whether patients truly had non-ischaemic aetiology is unknown, as routine coronary angiography or testing for myocardial ischaemia was not mandated. Similarly, thorough investigation for the cause of heart failure (for example with genetic testing and cardiac magnetic resonance imaging) was uncommon. Our large population from both observational studies and randomized trials emphasises that presumed DCM is very common in the young and very young. Close links with cardiac genetic services are useful for investigation of the index case and extended families.(172;173) Identification of abnormal cardiac structure and asymptomatic left ventricular dysfunction in family members permits risk stratification and treatment prior to the onset of symptoms of HF. Cardiovascular imaging, investigation for endocrine, nutritional and biochemical causes are mandatory, and myocardial biopsy should also be considered.(174) As anticipated, very few young patients have HF-PEF (e.g. 14% in those aged <40 years).

The preponderance of men in younger age groups was striking, with at least 70% males in every age category below 70 years, and was apparent in both cohort studies (52% of our patients) and randomized controlled trials (48%). More than half of the observational patient data originate from the Euro Heart Failure Survey and Italian Network on Congestive Heart Failure registry, which are broadly representative of patients hospitalised with HF or referred to HF clinics.(170;175) Peripartum cardiomyopathy should increase the proportion of women in younger age groups, though may have been underrepresented in cohort studies from hospitals without maternity services. Furthermore,

pharmacological trials often excluded pregnant or lactating women. Young women with HF are thus most likely underrepresented.

The preponderance of men in younger age groups is also reported in community echocardiographic studies,(34;39;47;51;176) epidemiology and large cohort studies of cardiomyopathy,(160;177) cardiomyopathy registries,(178;179) and genetic studies in patients with cardiomyopathy.(180-182) X-linked laminopathies and dystrophin defects such as Becker's and Duchenne's muscular dystrophy must contribute.(183;184) Dystrophin defects are most prevalent in younger (<30 years) men.(185) Certain mutations in cardiac troponin T or cardiac β-myosin heavy chain in patients with DCM result in early onset ventricular dysfunction and HF.(186;187) In patients with hypertrophic cardiomyopathy, men have more hypertrophy and a higher risk of left ventricular systolic dysfunction.(188) Arrhythmogenic right ventricular cardiomyopathy likewise exhibits a male preponderance with greater right ventricular dilatation.(189) Perhaps men preferentially inherit as yet unidentified genetic conditions causing dilated cardiomyopathy. A male preponderance of occult coronary disease and excess alcohol consumption is also possible. In addition, gender specific biological differences may play a role, including differences in cellular remodelling in response to wall stress e.g. after myocardial infarction.(190) Finally, the proportion of women rises sharply from around 70 years, suggesting survivorship (i.e. women's greater life expectancy) contributes. No matter the explanation, clinicians investigating young men with symptoms compatible with HF should be mindful to exclude the diagnosis.

4.4.2 Ejection fraction and medications

Young patients with HF have more severe left ventricular systolic dysfunction than their elderly counterparts, mandating therapy with ACEI, beta-blocker and spironolactone in most cases. Among the youngest patients in MAGGIC, prescribing rates of ACEI were 50% greater and beta-blocker rates almost double those observed in the elderly. While these differences are multifactorial, prescribing by indication and contraindication likely play a part: the prevalence of HF-REF is highest in the youngest, while comorbidities precluding therapy (e.g. chronic kidney disease and severe obstructive airways disease) are least prevalent in these patients. There are no evidence-based pharmacological treatments with prognostic benefit in HF-PEF.(5) The greater likelihood of patient with HF-REF

being managed in specialist cardiology services is associated with higher levels of pharmacotherapy.(146;170)

4.4.3 Symptoms

Despite having more severe left ventricular systolic dysfunction, younger patients in MAGGIC reported less marked symptoms as represented by NYHA class III/IV. NYHA functional class increased progressively with every decade. The DIG study reported similar findings (i.e. worse left ventricular systolic function but fewer symptoms in the young) albeit in a randomised clinical trial.(87) A small number of young patients with severe symptoms may have been excluded from our analysis and DIG due to listing for cardiac transplantation. Alternate reasons why younger patients have better NYHA functional class are incompletely understood, but may partly reflect fewer comorbidities such as atrial fibrillation or airways disease.

4.4.4 Outcomes

The three year mortality rate was relatively low in all age groups under the age of 60 years: 16.5%, 16.2% and 18.2% in those aged <40, 40-49 and 50-59 years respectively. Prior epidemiological studies have reported worse three years outcomes in younger age groups compared to our findings. In patients with HF aged 45-54 years in UK primary care followed from 1991, the 3 year mortality was 47% and 24% in men and women respectively.(168) Five-year mortality in patients aged <55 years was 39.4% in a previously hospitalised Scottish population studied from 1986-2003.(67) Conversely, the mortality rate in younger patients with HF is still significantly higher than the general population in the same age categories (death per 1000/year: 0.2 to 1.2 <40 years, 1.1 to 2.5 40-49 years and 2.6 to 6.2 in 50-59 years compared to our study 64.2 <40 years, 60.1 40-49 years and 73.2 50-59 years).(191;192)

The MAGGIC dataset includes 31 studies without EF as an inclusion criterion conducted over several decades. The deaths/1000 patient-years for the younger patients in the current analysis were similar among the RCTs and observational studies. The lower mortality rates in our dataset could reflect improved pharmacotherapies, but are unlikely to be a consequence of device-based therapies, as most of the included studies predate the increased uptake of device-based therapies for HF. The clinical relevance of our

observations is clear. Clinicians managing young patients with HF can inform and counsel patients appropriately, rather than citing outcomes from elderly cohorts. Patients need to know their predicted longer-term prognosis with modern medical and device therapy. To what extent these better outcomes are sustained is of interest. Mode of death was not included in MAGGIC (as it was not recorded in many of the included studies). Future studies should establish whether younger patients are more likely to die suddenly or from progressive pump failure. Potential therapeutic strategies to reduce mortality include implantable cardioverter defibrillators, cardiac resynchronisation therapy, ventricular assists devices, cardiac transplantation, and novel pharmacological agents. The impact of these strategies in part relates to the mode of death.

4.5 Limitations

A number of limitations merit consideration. The meta-analysis included individual patients' data from 31 randomised trials and observational studies, the variables collected being determined by each original study. Data on medications, NYHA functional class, echocardiographic and laboratory variables were not universally available in all patients. However, only variables with data available for at least 90% of the patients were included. Other important prognostic variables were not selected due to missing data, which could bias the analysis. The primary outcome, all-cause mortality, increases with age in part due to greater cardiovascular and non-cardiovascular comorbidity. However, too few studies provided cause-specific death to analyse cardiovascular death as opposed to all-cause mortality. The balance and competing risks between pump failure, sudden cardiac death, other cardiovascular death (e.g. myocardial infarction), and non-cardiovascular death are likely age dependent.

4.6 Conclusion

Younger patients with HF have different clinical profile including different aetiologies, more severe left ventricular dysfunction but less severe symptoms, and a lower three-year mortality. These differences are important to clinicians managing younger patients with H and also to younger patients with HF themselves who can be reassured by their dramatically better outcomes.

Chapter 5

Characteristics, treatment and outcomes of young adults newly diagnosed with heart failure: an analysis from the UK Clinical Practice Research Datalink.

5.1 Introduction

Around 900,000 people in the UK and 15 million people in Europe suffer from HF.(1;193) There are limited data with regards to how young patients differ from older patients with HF. Young patients with HF do appear to differ in several respects.

The U.K. Clinical Practice Research Datalink (CPRD) is a large and well-validated primary care database. 654 practices contribute information, covering approximately 8% of the UK population,(194-196) with 5.1 million active patients and 66 million person-years. The database records data on demographics, diagnoses, prescriptions, investigations, hospitalisations and mortality. This rich dataset offers an opportunity to investigate the characteristics and outcomes of young adults with heart failure.

Two previous studies have reported on HF using the CPRD dataset. The first excluded those under 45 years and predated (1991-1994) the widespread use of evidence-based pharmacological and device therapies.(20) The second described cases in 1996 only and was limited to reporting clinical characteristics. Patients aged less than 40 were not included.(197)

This study examines how young adults (aged less than 60 years) with HF differ from older adults with HF in the modern era, in terms of demographics, co-morbidities, treatment, and prognosis.

5.2 Methods

5.2.1 Dataset

This is a retrospective cohort study using data from the U.K. Clinical Practice Research Datalink (CPRD). The dataset is a large and well-validated primary care database with 654 practices contribute information, covering approximately 8% of the UK population. The diagnosis of HF in this dataset has previously been validated.

5.2.2 Study population

The study population consisted of all patients permanently registered with one of the 654 practices contributing to the November 2012 release of CPRD.

Patients with a first diagnosis of HF were identified after a 1-year screening period. The 1-year screening period provides adequate time to establish patients' baseline comorbidities and treatments before following them for an event in any newly registered patients with a practice. Similarly, in a newly registered practice with the CPRD, the 1-year screening period starts after the up-to-standard date, which is the date when the practice's records were deemed adequate for research purpose by the CPRD. HF was defined as a medical code for 'heart failure, cardiac failure, myocardial failure, cardiac dropsy, RV failure, LV failure, impaired LV function, weak heart, low output syndrome, cardiac asthma, cardiac insufficiency or myocardial insufficiency' in patient records. The accuracy of the U.K. CPRD diagnosis of HF has previously been validated.(198) The study cohort included all incident cases of HF who were at least 20 years of age at the time of diagnosis. The study population was stratified into 7 age categories: 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥80 years.

5.2.3 Medical codes used for HF

398,884,1223,2062,2906,4024,5141,5942,7251,9913,10079,10154,11424,12590,13189,15058,17278,18853,19066,21235,23481,23707,24503,26242,27679,27884,27964,32671,32898,32911,46672,46912,51214,68682,94870,8966,7321,558,11284,5155,5255,18793,12550,9524,11351,5293,22262,43618,26082,48466

5.2.4 Follow-up

The follow up period started with the date HF was diagnosed and ended with the earliest of date of death, date of leaving the practice or practice's last data collection date.

5.2.5 Outcomes and covariates

For each patient, the database for the most recent of the following prior to date of HF diagnosis was searched: heart rate, systolic blood pressure, diastolic blood pressure and body mass index (BMI); any history of cardiovascular disease, congenital heart disease, diabetes, thyroid disease, cancer, connective tissue disease, alcohol related disease, chronic kidney disease, COPD, asthma, anaemia, depression and cardiac procedure/surgery; the most recent smoking and alcohol status prior to the index date; and medication in the year prior to the index date. These baseline characteristics were summarised by age categories.

Prescription rates for ACEi or ARB, β blocker, and aldosterone antagonist between 2006 and 2011 and all cause mortality were summarised by age categories. I reported prescription rates between 2006 and 2011 to reflect the most contemporary prescribing practice.

5.2.6 Statistical analysis

Differences in baseline characteristics between age groups were tested using a generalised linear model with binomial errors for dichotomous data or normal errors for other data. For incident cases in 2006-11 prescription rates were estimated at 1, 3 and 6 months, and 1 and 5 years after diagnosis from Kaplan-Meier curves for each age group. All-cause mortality rates were estimated at 30 days and 1, 5, and 10 years from Kaplan-Meier curves for each age and sex group, separately for incident cases occurring in 1988-1993, 1994-1999, 2000-2005 and 2006-2011.

Adjusted hazard ratios for all-cause death were estimated for each age group relative to the 60-69 year group using proportional hazard models. A p value of <0.05 was considered statistically significant. All analyses were performed using SAS 9.1

5.3 Results

5.3.1 Baseline characteristics

Among 3 706 480 patients identified from the CPRD, there were 119,554 incident cases of HF in patients aged at least 20 years between 1988 and 2011. There were more men than women in all age groups below 80 year of age (Figure 5.1). Baseline characteristics are summarised in Table 5.1.

5.3.1.1 Heart rate, blood pressure, and body mass index

Younger patients had higher heart rates, lower blood pressures and lower body mass indices. (Table 5.1)

5.3.1.2 Comorbidities

Ischaemic heart disease, hypertension and valvular heart disease were less common in younger age groups (Table 5.1). Congenital heart disease and myocarditis were more common in the young. Atrial fibrillation, diabetes, and stroke were less common in younger age categories. Depression was more prevalent in the younger age groups. Among patients aged <60 years, chronic kidney disease was most prevalent in patients aged 20-29 years (7.9% 20-29 years, 6.3% 30-39 years, 4.1% 40-49 years, and 4.6% 50-59 years; p<0.001). A third of patients aged 20-29 years were diagnosed with asthma prior to

their index HF diagnosis. A history of pulmonary embolism was less common in the young.

5.3.1.3 Baseline medications

Despite the higher prevalence of depression in the youngest age group, the use of anti-depressants in younger patients was low. However, among patient aged <60 years, anti-psychotics were prescribed most frequently in patients aged 20-29 years (9.9% in 20-29 years vs. 6.6% in 50-59 years; $p<0.001$).

5.3.2 Prescription rates initiated after diagnosis of HF between 2006 and 2011

At all time points below 1 year, younger patients were less frequently prescribed ACEi or ARBs. The younger the patients the less often they received these therapies. (Table 5.2) Rates of β blocker prescriptions were also low. The 20-29 years group received less β blockers 5 years after diagnosis of HF. Aldosterone antagonists were similarly less often prescribed in younger age groups. For example, at 5 years 17.8% of patients aged 20-29 received aldosterone antagonists compared to 36.9% of those aged over 80.

Figure 5.1. Distribution of patients with newly diagnosed HF by age categories and sex.

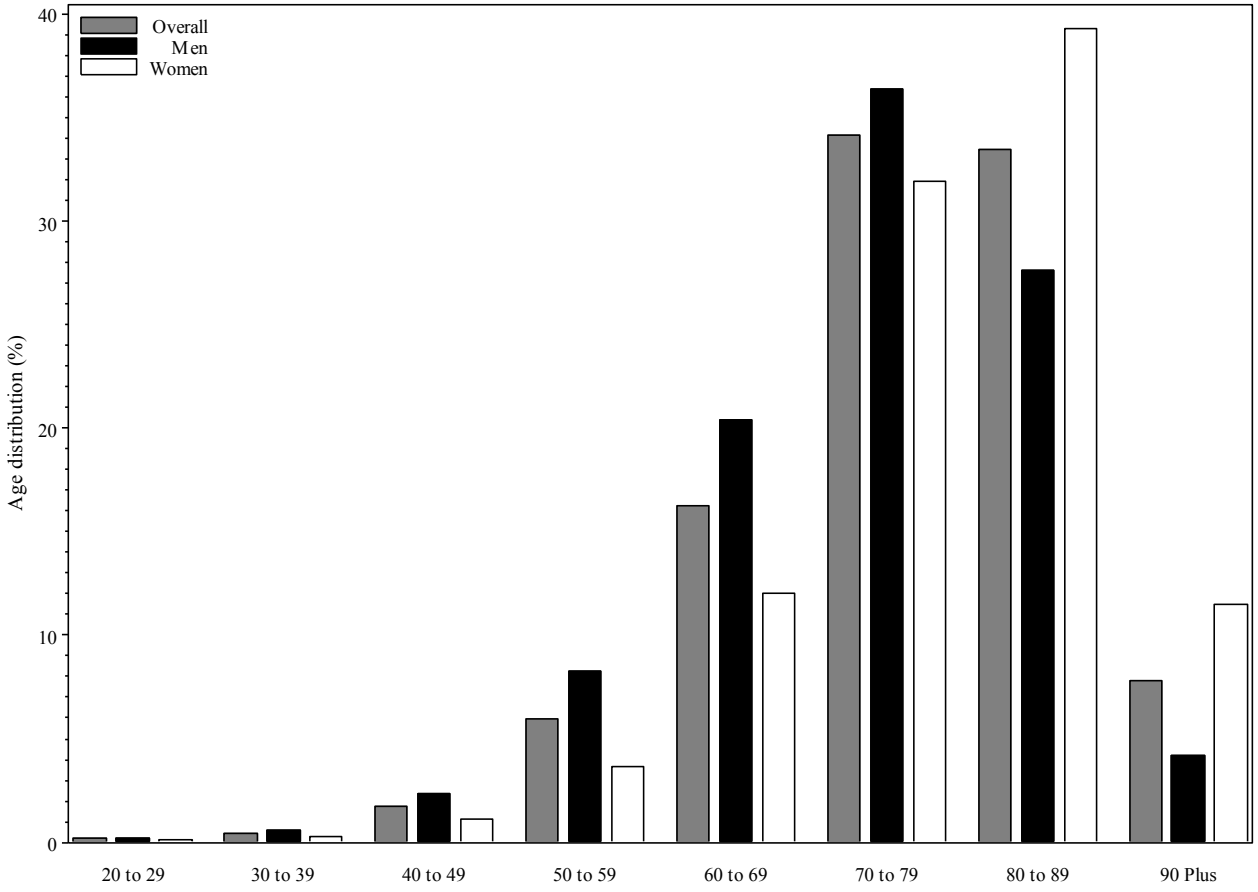


Table 5.1. Baseline characteristics at index diagnosis of HF by age.

		Age at diagnosis							
	N	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**≥ 80**	**P value**[1]
Demographic									
Cases	119,554	203	522	2,099	7,128	19,405	40,813	49,384	
Men (%)	50.1	55.7	64.2	68.1	69.4	63.0	53.4	38.7	
Examination (means)									
Heart rate (beats/min,)	24,044	85.5	83.9	83.3	80.4	78.2	76.9	76.0	<0.001
Systolic blood pressure (mmHg)	109,637	121.9	129.4	134.7	139.7	144.7	148.9	151.6	<0.001
Diastolic blood pressure (mmHg)	109,628	75.1	80.5	83.5	84.2	83.3	82.3	81.5	<0.001
Body mass index (kg/m^2)	86,110	25.8	28.7	29.8	29.6	28.8	27.5	26.0	<0.001
Comorbidities (%)									
Cardiovascular									
Ischaemic heart disease	39,793	5.9	12.5	24.8	33.7	38.7	36.6	29.1	<0.001
Hypertension	57,034	16.3	21.1	29.7	39.6	46.6	50.6	48.1	<0.001
Hyperlipidaemia	13,332	1.5	5.2	10.7	15.9	17.0	13.4	6.5	<0.001
Valvular heart disease	5,810	3.0	5.9	4.2	4.4	4.8	5.0	4.8	<0.001
Atrial fibrillation	22,358	4.4	9.0	10.2	12.8	16.1	19.3	20.6	<0.001
Myocarditis	112	2.0	1.1	0.8	0.4	0.1	0.0	0.0	<0.001
Stroke	18,695	3.9	3.3	4.1	7.6	11.7	15.5	19.2	<0.001
Pulmonary embolism	2,604	1.0	1.5	1.6	2.1	2.2	2.3	2.1	0.038
Peripheral arterial disease	9,859	2.0	1.1	2.5	5.5	8.8	9.7	7.6	<0.001
Congenital Heart Disease									
Any congenital heart disease	339	6.9	5.2	2.3	0.7	0.4	0.2	0.1	<0.001
Diabetes	19,729	9.4	13.8	15.7	19.2	21.4	18.7	12.5	<0.001
Any thyroid disease	9,501	3.0	5.0	4.4	5.2	6.6	8.0	9.0	<0.001
All cancer	10,407	3.0	3.8	3.3	4.3	6.2	9.1	10.3	<0.001
Connective tissue disease									
Any connective tissue disease	4,905	5.4	2.9	3.0	3.7	4.6	4.4	3.7	<0.001
Connective tissue disease	1,521	2.0	1.0	0.8	0.9	1.3	1.2	1.4	0.002
Rheumatoid arthritis	3,045	1.5	1.1	1.7	2.2	3.0	3.0	2.1	<0.001
Others									
Chronic kidney disease	11,587	7.9	6.3	4.1	4.6	6.5	9.4	12.2	<0.001
COPD	15,774	3.0	2.7	4.1	9.9	15.4	16.1	10.9	<0.001
Asthma	17,837	29.1	21.8	18.8	17.2	18.0	16.7	11.6	<0.001
Anaemia	16,555	6.9	8.0	8.4	7.0	8.9	12.7	18.1	<0.001
Depression	24,279	24.6	31.2	30.5	26.4	23.3	19.8	18.1	<0.001
Cardiac procedure/surgery									
PCI	2,197	1.5	1.1	3.4	3.4	3.2	2.0	0.8	<0.001
CABG	4,907	0.5	0.8	3.2	6.1	7.1	5.3	1.7	<0.001
Social history (%)									
Smoking status									
Current smoker	19,289	19.2	38.9	36.4	32.9	25.7	16.7	8.4	<0.001
Ex-smoker	29,479	9.4	12.6	18.8	25.3	29.5	27.8	20.5	<0.001
Alcohol status									
Heavy drinker	1,376	3.4	4.4	4.0	3.2	2.2	1.0	1,376	<0.001
Medications (%)									
Cardiovascular									
ACEi	35,672	22.2	29.9	34.2	35.7	35.0	31.4	25.5	<0.001
ARB	6,315	3.4	5.0	4.3	4.9	5.5	5.9	4.8	<0.001
ACEi or ARB	40,314	24.1	32.6	37.0	38.8	38.8	35.7	29.3	
B-blocker	11,372	10.8	13.8	15.2	13.3	12.0	9.6	7.7	<0.001
Aldosterone antagonist	4,889	5.9	5.9	7.0	5.4	4.6	3.9	3.7	<0.001

Diuretic	59,355	17.2	28.2	32.8	37.8	44.9	50.3	53.8	
Digoxin	15,831	5.9	6.5	6.4	8.5	10.4	13.1	15.6	<0.001
Isosorbide dinitrate + hydralazine	1,813	1.0	0.0	0.8	1.3	1.6	1.7	1.4	<0.001
Hydralazine	302	0.5	0.0	0.1	0.2	0.3	0.3	0.2	0.368
Isosorbide dinitrates	11,679	0.0	2.1	5.5	8.7	10.6	10.3	9.5	<0.001
Nicorandil	4,141	0.0	1.3	2.8	3.7	4.4	3.6	3.0	<0.001
Ivabradine	74	0.0	0.2	0.0	0.1	0.1	0.0	0.0	0.003
Warfarin	13,884	7.9	12.3	12.0	12.4	13.7	13.4	9.2	<0.001
Any anti-platelets	50,598	7.9	13.8	27.3	34.4	43.0	43.8	43.0	<0.001
Aspirin	48,157	7.9	13.6	26.3	32.8	41.0	41.6	40.9	<0.0001
Clopidogrel	5,373	0.0	2.1	5.1	5.7	5.2	4.6	4.0	<0.001
Dipyridamole	1,672	0.0	0.2	0.3	0.9	1.2	1.5	1.7	<0.001
Statin	28,992	3.9	13.6	23.2	30.7	32.8	28.1	17.0	<0.001
Calcium channel blockers	32,291	10.3	11.9	17.9	25.5	30.1	29.8	24.3	<0.0001
Amiodarone	4,146	3.4	4.0	2.8	3.9	4.1	3.9	2.8	<0.001
Diabetic									
Sulphonylureas	8,290	0.5	1.9	3.8	6.5	8.3	8.2	5.6	<0.001
Biguanides	8,301	0.0	5.2	6.5	10.0	10.7	8.2	4.1	<0.001
Thiazolidinediones	1,195	0.0	0.4	0.8	1.4	1.5	1.3	0.6	<0.001
Insulin	4,718	4.4	7.3	6.7	6.7	6.8	4.4	1.9	<0.001
Chronic airway disease									
β agonist	24,646	17.7	22.8	20.2	23.6	25.5	23.3	16.1	<0.001
Anti-muscarinic	10,065	1.0	1.9	3.9	7.8	10.5	10.2	6.5	<0.001
Theophylline	3,566	0.5	1.1	1.4	2.7	4.2	3.7	2.0	<0.001
Oxygen	1,806	3.4	1.0	1.0	1.3	1.9	1.8	1.2	<0.001
NSAIDs									
Non-selective NSAIDs	29,703	18.7	16.3	21.5	23.1	26.4	25.8	24.0	<0.001
Selective COX-2 inhibitors	2,934	2.0	1.3	1.7	2.0	2.4	2.5	2.5	0.004
Anti-depressants									
Tricyclic anti-depressants	11,725	4.4	7.3	11.4	10.8	10.5	9.8	9.3	<0.001
SSRIs	8,382	5.9	11.1	11.8	9.5	7.8	6.4	6.7	<0.001
Duloxetine	97	0.0	0.8	0.2	0.2	0.1	0.1	0.1	<0.001
Mirtazapine	729	0.5	2.1	0.8	0.9	0.5	0.5	0.6	<0.001
Venlafaxine	694	2.5	2.9	1.5	1.1	0.7	0.5	0.5	<0.001
Anti-psychotics									
Anti-psychotic drugs	10,412	9.9	8.2	7.5	6.6	6.8	7.8	10.5	<0.001

[1] From generalised linear models with binomial errors for dichotomous data or normal errors for other data.
ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; COPD=chronic obstructive pulmonary disease; COX-2=cyclooxygenase-2; NSAIDs=non-steroidal anti-inflammatory drugs; PCI=percutaneous coronary intervention;

Table 5.2. Prescription rates in patients with index diagnosis of HF between 2006-2011, including patients who had received the treatment prior to diagnosis.

% (95% CI)	Age at diagnosis						
	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	≥ 80
N	82	219	803	2252	5333	9964	12838
ACEi or ARB							
1 month	39.4 (28.7,50.0)	48.8 (42.2,55.5)	56.6 (53.2,60.1)	58.0 (56.0,60.1)	58.9 (57.6,60.2)	56.0 (55.1,57.0)	49.0 (48.1,49.8)
3 months	60.5 (49.8,71.2)	69.9 (63.7,76.0)	77.5 (74.6,80.4)	78.8 (77.1,80.5)	77.5 (76.3,78.6)	74.6 (73.7,75.4)	64.9 (64.0,65.7)
6 months	64.3 (53.8,74.8)	76.4 (70.6,82.2)	80.8 (78.0,83.6)	83.0 (81.5,84.6)	81.2 (80.2,82.3)	78.8 (78.0,79.6)	68.9 (68.0,69.7)
1 year	67.1 (56.7,77.4)	77.5 (71.8,83.2)	82.8 (80.2,85.5)	85.6 (84.1,87.1)	83.8 (82.7,84.8)	82.0 (81.2,82.8)	71.8 (71.0,72.7)
5 years	81.1 (68.0,94.2)	79.4 (73.7,85.0)	87.3 (84.5,90.0)	89.5 (88.0,91.0)	90.0 (88.9,91.0)	88.5 (87.6,89.4)	80.7 (79.5,82.0)
B-blocker							
1 month	25.8 (16.3,35.3)	35.9 (29.5,42.3)	39.6 (36.2,43.0)	38.8 (36.8,40.8)	34.6 (33.3,35.9)	30.2 (29.3,31.1)	25.3 (24.5,26.1)
3 months	41.9 (31.2,52.7)	52.7 (45.9,59.4)	56.0 (52.5,59.4)	53.2 (51.2,55.3)	47.9 (46.6,49.3)	43.3 (42.3,44.3)	35.6 (34.8,36.5)
6 months	45.8 (34.9,56.7)	57.2 (50.5,63.9)	60.3 (56.9,63.7)	57.8 (55.8,59.9)	53.2 (51.8,54.5)	48.2 (47.2,49.2)	39.4 (38.5,40.3)
1 year	49.9 (38.9,61.0)	60.4 (53.8,67.1)	63.6 (60.2,67.0)	61.8 (59.8,63.9)	57.6 (56.3,59.0)	52.3 (51.3,53.3)	43.0 (42.1,43.9)
5 years	57.6 (46.3,68.8)	69.7 (62.6,76.8)	73.4 (69.8,77.0)	70.9 (68.7,73.0)	69.7 (68.2,71.2)	66.9 (65.6,68.1)	57.8 (56.3,59.2)
Aldosterone antagonist							
1 month	6.2 (0.9,11.4)	14.3 (9.6,18.9)	16.3 (13.7,18.9)	14.0 (12.6,15.5)	13.1 (12.2,14.0)	11.7 (11.1,12.3)	11.0 (10.5,11.6)
3 months	13.6 (6.1,21.0)	21.8 (16.3,27.3)	24.2 (21.2,27.2)	20.9 (19.2,22.6)	20.2 (19.2,21.3)	17.8 (17.0,18.5)	17.1 (16.4,17.7)
6 months	14.8 (7.1,22.6)	25.7 (19.9,31.6)	26.7 (23.6,29.8)	23.9 (22.2,25.7)	23.4 (22.3,24.6)	21.0 (20.2,21.9)	20.1 (19.3,20.8)
1 year	16.2 (8.1,24.2)	27.3 (21.3,33.3)	30.2 (27.0,33.4)	27.5 (25.6,29.4)	27.0 (25.8,28.3)	24.4 (23.5,25.3)	23.6 (22.8,24.4)
5 years	17.8 (9.3,26.2)	36.2 (29.1,43.4)	38.6 (34.7,42.6)	36.6 (34.2,38.9)	38.9 (37.3,40.6)	37.8 (36.5,39.1)	36.9 (35.5,38.2)
Digoxin							
1 month	2.4 (0.0, 5.8)	6.9 (3.5,10.3)	9.0 (7.0,11.0)	9.0 (7.9,10.2)	10.9 (10.1,11.8)	13.5 (12.8,14.1)	16.4 (15.8,17.1)
3 months	7.4 (1.7,13.1)	9.8 (5.8,13.7)	12.5 (10.2,14.8)	12.6 (11.2,13.9)	15.9 (14.9,16.8)	18.8 (18.1,19.6)	22.8 (22.1,23.5)
6 months	8.6 (2.5,14.8)	9.8 (5.8,13.7)	13.8 (11.4,16.2)	13.8 (12.3,15.2)	17.5 (16.4,18.5)	20.7 (19.9,21.5)	24.7 (24.0,25.5)
1 year	10.0 (3.4,16.5)	10.8 (6.6,15.0)	14.4 (12.0,16.9)	15.0 (13.5,16.4)	19.2 (18.1,20.2)	22.4 (21.6,23.3)	26.5 (25.7,27.3)
5 years	10.0 (3.4,16.5)	14.3 (8.9,19.6)	18.0 (15.1,21.0)	20.1 (18.2,22.0)	24.4 (23.1,25.7)	29.6 (28.5,30.7)	35.1 (33.8,36.4)

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval.

5.3.3 Mortality

Mortality rates following a diagnosis of HF improved over the last two decades in all age groups. (Table 5.3) Since 2000, 1 and 5 year mortality rates have generally been lowest in younger patients and increased with age, rising more sharply from 50 years of age. After multivariate adjustment, patients aged 30-39 years had the lowest risk of death [HR 0.49 (95% CI: 0.40-0.61)] compared to the reference age group 60-69 years. (Table 5.4) The youngest men are an exception. Men aged 20-29 years had a similar risk of death to the reference age group 60-69 years [HR 1.02 (95% CI: 0.72-1.45)], which was significantly greater than men aged 30-39 and 40-49 years.

Table 5.3. Mortality stratified by sex, year, and age.

% (95% CI)	Age group						
	20 to 29	**30 to 39**	**40 to 49**	**50 to 59**	**60 to 69**	**70 to 79**	**≥ 80**
Men							
1988-1993, N	17	14	102	426	1425	2469	1868
1994-1999, N	10	46	243	1051	2889	5648	4392
2000-2005, N	42	120	512	1818	4286	7794	6937
2006-2011, N	44	155	573	1650	3619	5880	5910
30 days							
1988-1993	35.3 (12.6,58.0)	21.4 (0.0,42.9)	13.7 (7.0,20.4)	11.5 (8.5,14.5)	10.7 (9.1,12.4)	13.1 (11.8,14.4)	15.9 (14.2,17.6)
1994-1999	20.0 (0.0,44.8)	32.6 (19.1,46.2)	11.5 (7.5,15.5)	12.0 (10.0,14.0)	9.4 (8.4,10.5)	12.0 (11.2,12.9)	16.4 (15.3,17.5)
2000-2005	4.8 (0.0,11.2)	3.3 (0.1, 6.6)	4.7 (2.9, 6.5)	5.6 (4.6, 6.7)	5.6 (4.9, 6.2)	7.6 (7.0, 8.2)	12.6 (11.9,13.4)
2006-2011	4.5 (0.0,10.7)	5.2 (1.7, 8.7)	4.9 (3.1, 6.7)	4.4 (3.4, 5.4)	4.2 (3.6, 4.9)	4.9 (4.4, 5.5)	11.3 (10.5,12.1)
1 year							
1988-1993	47.1 (23.3,70.8)	35.7 (10.6,60.8)	22.7 (14.5,30.9)	20.1 (16.3,23.9)	25.1 (22.9,27.4)	31.8 (30.0,33.7)	38.0 (35.8,40.2)
1994-1999	30.0 (1.6,58.4)	34.9 (21.1,48.6)	17.0 (12.2,21.7)	19.8 (17.4,22.2)	21.5 (20.0,23.0)	28.5 (27.3,29.7)	38.1 (36.6,39.5)
2000-2005	14.6 (3.8,25.5)	5.9 (1.7,10.1)	9.6 (7.1,12.2)	12.2 (10.7,13.7)	15.4 (14.3,16.5)	22.5 (21.5,23.4)	34.6 (33.5,35.7)
2006-2011	11.5 (2.0,21.0)	7.8 (3.6,12.0)	7.1 (5.0, 9.2)	8.9 (7.5,10.2)	11.8 (10.7,12.8)	16.5 (15.5,17.4)	32.7 (31.4,33.9)
5 years							
1988-1993	66.9 (43.8,90.0)	35.7 (10.6,60.8)	40.6 (30.8,50.4)	42.0 (37.2,46.8)	53.2 (50.6,55.9)	66.1 (64.2,68.0)	79.3 (77.3,81.3)
1994-1999	64.0 (32.4,95.6)	54.4 (39.5,69.4)	33.9 (27.7,40.0)	38.8 (35.8,41.8)	46.6 (44.7,48.4)	61.8 (60.5,63.1)	78.2 (76.9,79.6)
2000-2005	23.3 (9.8,36.7)	22.0 (14.0,30.0)	20.4 (16.8,24.1)	27.0 (24.9,29.1)	37.2 (35.7,38.7)	53.3 (52.2,54.5)	74.7 (73.6,75.8)
2006-2011	14.1 (3.6,24.6)	13.6 (7.4,19.7)	18.4 (14.3,22.6)	20.1 (17.6,22.5)	31.5 (29.5,33.4)	46.5 (44.8,48.3)	71.7 (70.0,73.4)
10 years							
1988-1993	73.5 (51.7,95.4)	63.3 (35.7,90.9)	59.4 (49.2,69.5)	62.0 (57.1,66.8)	73.9 (71.5,76.3)	87.1 (85.6,88.5)	95.9 (94.8,97.0)
1994-1999	82.0 (52.5, 100)	60.0 (45.0,74.9)	46.1 (39.4,52.7)	55.0 (51.8,58.2)	69.1 (67.3,70.9)	83.5 (82.4,84.6)	95.3 (94.5,96.1)
2000-2005		32.5 (21.8,43.1)	29.8 (25.1,34.6)	41.3 (38.6,44.1)	58.7 (56.9,60.6)	77.5 (76.3,78.8)	93.4 (92.5,94.3)
Women							
1988-1993, N	5	13	48	246	986	2593	3464
1994-1999, N	16	34	125	504	1914	5411	7953
2000-2005, N	28	63	235	757	2405	6597	10868
2006-2011, N	41	77	261	676	1881	4421	7992
30 days							
1988-1993	20.0 (0.0,55.1)	15.4 (0.0,35.0)	18.8 (7.7,29.8)	7.7 (4.4,11.1)	11.1 (9.1,13.0)	11.7 (10.5,13.0)	17.5 (16.2,18.7)
1994-1999	12.5 (0.0,28.7)	8.8 (0.0,18.4)	18.5 (11.6,25.3)	10.5 (7.8,13.2)	10.0 (8.6,11.3)	10.5 (9.7,11.4)	16.2 (15.4,17.0)
2000-2005	3.6 (0.0,10.4)	1.6 (0.0, 4.7)	8.5 (4.9,12.1)	4.6 (3.1, 6.1)	5.9 (5.0, 6.9)	7.5 (6.9, 8.2)	12.9 (12.3,13.6)
2006-2011	4.9 (0.0,11.5)	7.8 (1.8,13.8)	3.8 (1.5, 6.2)	4.1 (2.6, 5.6)	4.8 (3.9, 5.8)	5.6 (4.9, 6.3)	12.8 (12.1,13.6)
1 year							
1988-1993	40.0	15.4	22.9	17.2	22.5	24.4	35.7

	(0.0,82.9)	(0.0,35.0)	(11.0,34.8)	(12.5,22.0)	(19.9,25.2)	(22.7,26.1)	(34.0,37.3)
1994-1999	19.8	21.0	28.2	19.1	19.8	23.7	34.5
	(0.0,40.0)	(7.1,34.8)	(20.3,36.1)	(15.7,22.6)	(18.1,21.6)	(22.6,24.9)	(33.5,35.6)
2000-2005	11.5	9.7	12.8	10.7	14.2	19.1	32.0
	(0.0,23.7)	(2.3,17.0)	(8.5,17.1)	(8.5,12.9)	(12.8,15.6)	(18.1,20.0)	(31.1,32.9)
2006-2011	9.9	10.6	9.7	9.6	12.4	16.9	32.8
	(0.7,19.1)	(3.7,17.6)	(6.1,13.3)	(7.3,11.8)	(10.9,13.9)	(15.8,18.0)	(31.8,33.9)
5 years							
1988-1993	40.0	15.4	37.4	33.8	45.8	52.9	72.9
	(0.0,82.9)	(0.0,35.0)	(23.2,51.6)	(27.7,39.9)	(42.6,49.0)	(50.9,54.9)	(71.3,74.5)
1994-1999	36.2	31.1	36.7	35.9	41.6	50.8	70.0
	(10.1,62.3)	(14.9,47.2)	(28.1,45.2)	(31.6,40.3)	(39.3,43.9)	(49.4,52.2)	(68.9,71.1)
2000-2005	28.3	17.4	25.0	26.4	34.2	45.9	68.7
	(10.5,46.2)	(7.5,27.3)	(19.3,30.7)	(23.1,29.7)	(32.3,36.2)	(44.6,47.1)	(67.8,69.7)
2006-2011	14.2	15.5	19.1	23.6	32.0	40.8	68.7
	(2.2,26.2)	(6.2,24.7)	(13.2,24.9)	(19.3,27.8)	(29.3,34.8)	(38.9,42.8)	(67.2,70.2)
10 years							
1988-1993	40.0	32.3	47.2	50.0	65.5	75.4	91.5
	(0.0,82.9)	(6.1,58.5)	(32.3,62.1)	(43.3,56.7)	(62.3,68.7)	(73.6,77.2)	(90.3,92.6)
1994-1999	57.5	40.3	51.1	52.2	60.6	73.9	90.9
	(19.3,95.7)	(21.9,58.8)	(41.9,60.4)	(47.5,56.9)	(58.2,63.0)	(72.6,75.2)	(90.1,91.7)
2000-2005	34.8	24.1	36.4	44.7	54.7	69.0	89.8
	(14.5,55.1)	(12.4,35.8)	(29.2,43.7)	(40.5,49.0)	(52.2,57.1)	(67.6,70.4)	(89.0,90.7)

CI=confidence interval.

Table 5.4. Hazard ratios (HR) by age categories and sex for all cause death

		Age group											
		20 to 29		**30 to 39**		**40 to 49**		**50 to 59**		**60 to 69**		**70 to 79**	**≥ 80**
		N	HR (95%CI)	N	HR (95%CI)	N	HR (95%CI)	N	HR (95%CI)	N	HR	N	HR (95%CI)	N	HR (95%CI)
All deaths															
Unadjusted	Male	31	0.98 (0.69,1.40)	57	0.52 (0.40,0.68)	261	0.49 (0.43,0.55)	1,247	0.66 (0.62,0.71)	4,150	1	9,401	1.57 (1.52,1.63)	9,483	2.63 (2.53,2.73)
	Female	14	0.57 (0.34,0.96)	27	0.45 (0.31,0.66)	147	0.67 (0.57,0.79)	535	0.70 (0.64,0.77)	2,352	1	7,541	1.42 (1.36,1.49)	14,630	2.60 (2.49,2.72)
Adjusted for covariates	Male	31	1.02 (0.72,1.45)	57	0.52 (0.40,0.68)	261	0.50 (0.44,0.57)	1,247	0.68 (0.64,0.72)	4,150	1	9,401	1.54 (1.49,1.60)	9,483	2.55 (2.46,2.65)
	Female	14	0.56 (0.33,0.94)	27	0.43 (0.30,0.63)	147	0.66 (0.56,0.78)	535	0.70 (0.64,0.77)	2,352	1	7,541	1.43 (1.36,1.50)	14,630	2.63 (2.52,2.76)

CI=confidence interval; N=total number of death.

5.4 Discussion

In this large primary care database with nearly 10,000 patients younger than 60 years, I have demonstrated important differences from older patients with HF, namely aetiology, comorbidities, HF treatment rates, and mortality rates.

5.4.1 Heart rates

Prior to first presentation with heart failure younger patients had higher heart rates. Perhaps the lack of ankle oedema and crackles in younger patients (previously described by our group in the CHARM dataset) means that diagnosis is delayed and, consequently, the patient is sicker with a higher heart rate.(199)

5.4.2 Comorbidities

As previously described, coronary heart disease, hypertension and valvular heart disease are less common in younger age groups. Congenital heart disease accounted for 6.9% of cases of heart failure in patients aged 20-29. This proportion increased over 2 decades (0.0% in 1988-1992 to 8.6% in 2008-2011) in patients aged 20-29. Myocarditis, although still an uncommon cause of HF in the young, was a more frequent prior diagnosis in younger adults with HF. Experimental studies suggest that testosterone might play a major role in the development of myocarditis by increases viral binding, modification of immune system, inhibition of anti-inflammatory cells, and increases cardiac fibrosis genes expression.(200;201) Myocardial fibrosis measured by Cardiac Magnetic Resonance (CMR) Imaging in patients with acute myocarditis was more frequent and more severe in patients aged <40 years.(202)

A diagnosis of depression was more common in younger adults with HF, occurring in approximately a quarter to a third of patients. These findings concur with a previous study of depression in hospitalised patients with HF, in which younger age was an

independent predictor of depression across all New York Heart Association functional classes (age <60 vs. ≥60 years HR 1.95 [95% CI 1.36-2.81], p=0.0003).(203) Younger patients with HF are recognised to have worse quality of life.(199) This greater functional limitation, resulting in an inability to meet family and social commitments, may to some extent explain the greater prevalence of depression. Anti-psychotics are most frequently taken by patients aged 20-29. Clozapine and other antipsychotics are known to cause HF. How often these drugs are causative is currently unclear.

A third of the patients aged 20-29 years had a diagnosis of asthma at index diagnosis of HF. To provide context, the lifetime prevalence of asthma was much lower in a study utilising CPRD data from 422 primary care practices in England (Age-sex standardised rate: 15-44 years 12.7%, 45-64 years 9.1%, and >65 years 9.6%).(204) HF may be incorrectly labelled as asthma for many reasons. Younger patients are not expected to have HF. They also present with breathlessness and cough, with fewer classical signs of HF such as crepitation or peripheral oedema.(199) Misdiagnosis may not be the only reason for this finding. The use of β agonists in patients with pulmonary disease is also associated with incident HF and increased HF hospitalisation.(205) Oral bambuterol was associated with an increased incident of HF compared with the reference drug nedocromil (age and sex adjusted relative risk: 3.41 [95% CI: 1.99 to 5.86]; p<0.0001).(206) Similarly, patients with COPD receiving β agonists have an increased risk of HF hospitalisation in a nested case control analysis comparing patients who inhaled respiratory drugs with and without cardiovascular events using the Manitoba Health database between 1996 and 200.(207) Perhaps chronic beta-receptor stimulation induces adverse remodelling, the opposite of beta-blocker effects. Sustained tachycardia associated with prolonged exposure to β agonists may also increase the risk of HF and related adverse outcome.

5.4.3 Treatments

Between 2006 and 2011, patients aged 20-29 years had the lowest treatment rates for ACEi/ARB, β blocker, and aldosterone antagonist. Why this should be is difficult to explain. The higher proportions of chronic kidney disease and asthma may have deterred clinicians from optimising HF medications in the younger patients (Table 5.5, and 5.6).

Previous studies reported higher proportions of younger patients were prescribed HF medications between 2005 and 2007.(69;82;93) However, these studies defined 'young' as less than 60 to 65 years and may reveal similar findings to ours if patients less than 60 to 65 years were stratified into more than one group. Grouping patients < 60 years in our cohort demonstrated higher prescription rates for HF medications in younger patients congruent with previous studies. (Table 5.7)

5.4.4 Mortality

Mortality rates in younger age groups were dramatically lower compared to older patients. A recent Swedish study reported a 1 year mortality rate of 12.2% in age group 18-34 years, 10.6% in 35-44 years, 12.2% in 45-54 years, and 26.6% in 55-84 years between 2002 and 2006.(17) In comparison, between 2006 and 2011, I reported a 1-year mortality rates of 10.7% in age group 20-29 years, 8.8% in 30-39 years, 7.9% in 40-49 years, 9.1% in 50-59 years, 12.0% in 60-69 years, 16.6% in 70-79 years, and 32.8% in those aged ≥80 years. For comparison, the annual mortality rates for the population of England and Wales in 2011 across the respective age bands was: 0.05%, 0.08%, 0.18%, 0.42%, 1.02%, 2.80%, and 10.43%. The mortality rates in patients with HF were substantially higher. Five-year mortality rates have continued to improve albeit to a lesser degree in those aged ≥70 years. Improving uptake of pharmacological and device therapy may further reduce mortality and morbidity, particularly in the younger age group. Physicians can now reassure younger patients of their better prognosis with these data.

5.5 Limitations

Although this study was conducted using a large well-validated database, a few limitations merit consideration. I relied on physician diagnoses or documentation of heart failure, comorbidities, and risk factors without independent confirmation of diagnoses or data on left ventricular ejection fraction. The prevalence of co-morbidities (e.g. ischaemic heart disease, hypertension, diabetes, etc.) may be lower than expected. The recording of these co-morbidities was less systematic prior to the introduction of the Quality and

Outcomes Framework (QOF) in 2004, which reimburses general practices for specifying this information. However, previous studies have validated the accuracy of these diagnoses in CPRD.(198) However, the study validating HF code in this study did not include younger patients less than 35 years. The numbers in the younger age groups were small with wide confidence interval resulting in greater uncertainty when interpreting results.

5.6 Conclusion

Younger adults with HF have different characteristics including different aetiologies, comorbidities, lower treatment rates and lower mortality rates. Between 1988 and 2011, mortality rates have continued to improve in all age groups.

Table 5.5. Prescription rates in patients with index diagnosis of HF between 2006-2011 and with asthma, including patients who had received the treatment prior to diagnosis.

% (95% CI)	Age at diagnosis						
	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 plus
N	25	51	179	395	1001	1872	1813
ACEi or ARB							
1 month	32.0 (13.7,50.3)	45.1 (31.4,58.8)	57.8 (50.6,65.1)	56.2 (51.3,61.1)	59.7 (56.6,62.7)	55.3 (53.1,57.6)	50.3 (48.0,52.7)
3 months	52.0 (32.4,71.6)	62.7 (49.5,76.0)	77.6 (71.5,83.8)	76.3 (72.1,80.6)	77.0 (74.3,79.6)	72.6 (70.6,74.7)	66.4 (64.1,68.6)
6 months	56.0 (36.5,75.5)	71.0 (58.5,83.6)	82.3 (76.7,88.0)	80.0 (76.0,84.0)	80.4 (77.9,82.9)	76.9 (75.0,78.9)	70.2 (67.9,72.4)
1 year	56.0 (36.5,75.5)	73.1 (60.8,85.4)	83.6 (78.1,89.1)	81.7 (77.8,85.6)	82.8 (80.4,85.3)	80.6 (78.7,82.4)	72.7 (70.5,74.9)
5 years	73.6 (55.9,91.3)	-(0.0, 100)	89.3 (83.5,95.2)	85.7 (81.9,89.5)	91.7 (89.1,94.3)	87.4 (85.3,89.5)	81.4 (78.6,84.3)
B-blocker							
1 month	12.0 (0.0,24.7)	31.4 (18.6,44.1)	30.3 (23.6,37.1)	26.2 (21.8,30.5)	20.0 (17.5,22.4)	18.7 (17.0,20.5)	16.2 (14.5,18.0)
3 months	24.0 (7.3,40.7)	45.2 (31.5,58.8)	44.6 (37.2,51.9)	36.8 (32.0,41.5)	28.0 (25.2,30.8)	26.5 (24.5,28.5)	23.2 (21.2,25.2)
6 months	32.4 (13.9,51.0)	53.3 (39.5,67.1)	49.2 (41.8,56.6)	40.2 (35.4,45.1)	32.6 (29.6,35.5)	30.5 (28.4,32.6)	25.8 (23.7,27.9)
1 year	32.4 (13.9,51.0)	53.3 (39.5,67.1)	51.1 (43.7,58.5)	44.7 (39.8,49.7)	36.0 (33.0,39.1)	33.5 (31.3,35.7)	28.7 (26.5,30.9)
5 years	51.4 (30.6,72.1)	56.4 (42.3,70.5)	69.5 (58.8,80.2)	52.4 (46.6,58.2)	52.0 (47.8,56.1)	48.0 (44.9,51.1)	45.6 (41.2,49.9)
Aldosterone antagonist							
1 month	8.0 (0.0,18.6)	11.8 (2.9,20.6)	16.8 (11.3,22.3)	14.0 (10.6,17.4)	15.0 (12.8,17.3)	12.8 (11.3,14.3)	12.0 (10.5,13.5)
3 months	12.0 (0.0,24.7)	15.7 (5.7,25.7)	27.1 (20.5,33.6)	23.0 (18.8,27.2)	21.8 (19.3,24.4)	19.5 (17.7,21.3)	18.4 (16.5,20.2)
6 months	12.0 (0.0,24.7)	23.7 (12.0,35.4)	32.4 (25.5,39.3)	26.4 (22.1,30.8)	24.8 (22.1,27.5)	22.5 (20.6,24.5)	22.0 (20.0,24.0)
1 year	12.0 (0.0,24.7)	28.0 (15.5,40.4)	36.1 (28.9,43.2)	29.8 (25.2,34.4)	28.7 (25.8,31.6)	26.8 (24.7,28.9)	25.5 (23.4,27.6)
5 years	16.6 (1.7,31.6)	39.0 (24.4,53.6)	44.0 (35.3,52.8)	38.5 (33.1,43.9)	41.5 (37.6,45.4)	40.8 (37.8,43.8)	38.0 (34.6,41.4)
Digoxin							
1 month	8.0 (0.0,18.6)	9.8 (1.6,18.0)	11.8 (7.1,16.5)	11.7 (8.5,14.9)	13.0 (10.9,15.1)	15.7 (14.1,17.4)	17.8 (16.0,19.6)
3 months	16.0 (1.6,30.4)	9.8 (1.6,18.0)	15.2 (9.9,20.5)	14.8 (11.3,18.3)	18.6 (16.2,21.0)	21.5 (19.6,23.4)	24.6 (22.5,26.6)
6 months	16.0 (1.6,30.4)	9.8 (1.6,18.0)	17.0 (11.4,22.5)	15.6 (12.0,19.2)	20.1 (17.6,22.6)	23.6 (21.6,25.5)	26.2 (24.1,28.2)
1 year	16.0 (1.6,30.4)	9.8 (1.6,18.0)	17.6 (12.0,23.2)	17.0 (13.2,20.7)	22.2 (19.6,24.9)	25.4 (23.4,27.4)	28.0 (25.9,30.2)
5 years	16.0 (1.6,30.4)	15.8 (2.1,29.5)	23.3 (15.7,31.0)	21.9 (17.4,26.4)	28.7 (25.4,31.9)	33.7 (30.9,36.4)	37.3 (34.1,40.6)

Table 5.6. Prescription rates in patients with index diagnosis of HF between 2006-2011 and with chronic kidney disease, including patients who had received the treatment prior to diagnosis.

% (95% CI)	Age at diagnosis						
	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 plus
N	6	13	49	205	855	2840	4764
ACEi or ARB							
1 month	50.0 (10.0,90.0)	46.2 (19.1,73.3)	48.3 (34.1,62.6)	51.7 (44.8,58.6)	51.5 (48.1,54.8)	53.5 (51.7,55.3)	49.1 (47.7,50.6)
3 months	50.0 (10.0,90.0)	76.9 (54.0,99.8)	59.3 (45.2,73.4)	69.3 (62.9,75.8)	72.7 (69.6,75.7)	72.3 (70.6,74.0)	64.9 (63.5,66.3)
6 months	66.7 (28.9, 100)	76.9 (54.0,99.8)	61.6 (47.6,75.6)	72.9 (66.6,79.2)	75.3 (72.3,78.3)	76.9 (75.3,78.5)	68.8 (67.5,70.2)
1 year	66.7 (28.9, 100)	84.6 (65.0, 100)	63.8 (50.0,77.7)	76.0 (69.8,82.1)	78.1 (75.2,81.0)	80.3 (78.8,81.9)	71.6 (70.2,73.0)
5 years	-(0.0, 100)	-(0.0, 100)	-(0.0, 100)	80.3 (72.9,87.7)	87.2 (83.9,90.4)	87.7 (85.8,89.6)	79.5 (77.6,81.4)
B-blocker							
1 month	33.3 (0.0,71.1)	23.1 (0.2,46.0)	37.2 (23.6,50.8)	39.4 (32.6,46.1)	34.4 (31.2,37.6)	33.4 (31.6,35.1)	28.4 (27.1,29.7)
3 months	33.3 (0.0,71.1)	30.8 (5.7,55.9)	43.6 (29.5,57.6)	51.2 (44.3,58.2)	47.0 (43.6,50.4)	47.3 (45.4,49.1)	39.4 (38.0,40.8)
6 months	33.3 (0.0,71.1)	38.5 (12.0,64.9)	54.4 (40.2,68.6)	56.3 (49.3,63.2)	53.3 (49.9,56.7)	51.2 (49.4,53.1)	43.1 (41.7,44.6)
1 year	33.3 (0.0,71.1)	38.5 (12.0,64.9)	58.8 (44.7,72.8)	61.7 (54.8,68.7)	58.4 (55.0,61.8)	55.6 (53.7,57.5)	46.8 (45.3,48.3)
5 years	. (0.0, 100)	70.7 (40.7, 100)	66.9 (51.2,82.5)	74.1 (67.0,81.1)	72.3 (67.8,76.7)	68.5 (65.9,71.2)	62.0 (59.5,64.5)
Aldosterone antagonist							
1 month	16.7 (0.0,46.5)	30.8 (5.7,55.9)	10.5 (1.8,19.2)	10.8 (6.5,15.1)	14.7 (12.3,17.1)	11.8 (10.6,13.0)	11.1 (10.2,12.0)
3 months	16.7 (0.0,46.5)	38.5 (12.0,64.9)	12.6 (3.2,22.0)	15.5 (10.5,20.5)	21.5 (18.7,24.2)	18.2 (16.8,19.6)	17.3 (16.2,18.4)
6 months	16.7 (0.0,46.5)	38.5 (12.0,64.9)	14.8 (4.7,24.9)	18.1 (12.8,23.5)	24.3 (21.4,27.2)	21.5 (19.9,23.0)	20.4 (19.2,21.6)
1 year	16.7 (0.0,46.5)	38.5 (12.0,64.9)	19.2 (7.9,30.5)	22.1 (16.2,28.0)	27.1 (24.1,30.2)	24.9 (23.2,26.5)	23.8 (22.5,25.1)
5 years	-(0.0, 100)	38.5 (12.0,64.9)	31.8 (12.8,50.9)	27.8 (20.9,34.8)	40.0 (35.5,44.5)	39.3 (36.6,41.9)	38.0 (35.5,40.5)
Digoxin							
1 month	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	6.2 (0.0,13.0)	7.4 (3.8,11.0)	8.7 (6.8,10.6)	12.6 (11.4,13.9)	15.2 (14.2,16.3)
3 months	0.0 (0.0, 0.0)	7.7 (0.0,22.2)	8.3 (0.5,16.2)	10.5 (6.2,14.7)	14.0 (11.7,16.4)	17.6 (16.2,19.0)	20.6 (19.4,21.8)
6 months	0.0 (0.0, 0.0)	7.7 (0.0,22.2)	8.3 (0.5,16.2)	11.0 (6.7,15.3)	15.8 (13.3,18.3)	19.6 (18.1,21.1)	22.2 (21.0,23.5)
1 year	0.0 (0.0, 0.0)	7.7 (0.0,22.2)	8.3 (0.5,16.2)	12.6 (8.0,17.3)	18.7 (16.0,21.3)	21.2 (19.7,22.7)	23.9 (22.6,25.1)
5 years	-(0.0, 100)	7.7 (0.0,22.2)	8.3 (0.5,16.2)	14.8 (9.7,19.9)	25.2 (21.3,29.1)	29.5 (27.2,31.8)	32.6 (30.3,35.0)

Table 5.7. Prescription rates in patients with index diagnosis of HF between 2006-2011, including patients who had received the treatment prior to diagnosis

% (95% CI)	Age at diagnosis			
	<60	60 to 69	70 to 79	80 plus
N	3356	5333	9964	12838
ACEi or ARB				
1 month	56.6 (55.0,58.3)	58.9 (57.6,60.2)	56.0 (55.1,57.0)	49.0 (48.1,49.8)
3 months	77.5 (76.0,78.9)	77.5 (76.3,78.6)	74.6 (73.7,75.4)	64.9 (64.0,65.7)
6 months	81.6 (80.3,82.9)	81.2 (80.2,82.3)	78.8 (78.0,79.6)	68.9 (68.0,69.7)
1 year	84.0 (82.7,85.3)	83.8 (82.7,84.8)	82.0 (81.2,82.8)	71.8 (71.0,72.7)
5 years	88.2 (86.9,89.5)	90.0 (88.9,91.0)	88.5 (87.6,89.4)	80.7 (79.5,82.0)
B-blocker				
1 month	38.5 (36.9,40.2)	34.6 (33.3,35.9)	30.2 (29.3,31.1)	25.3 (24.5,26.1)
3 months	53.6 (51.9,55.3)	47.9 (46.6,49.3)	43.3 (42.3,44.3)	35.6 (34.8,36.5)
6 months	58.1 (56.4,59.8)	53.2 (51.8,54.5)	48.2 (47.2,49.2)	39.4 (38.5,40.3)
1 year	61.9 (60.2,63.6)	57.6 (56.3,59.0)	52.3 (51.3,53.3)	43.0 (42.1,43.9)
5 years	71.1 (69.3,72.9)	69.7 (68.2,71.2)	66.9 (65.6,68.1)	57.8 (56.3,59.2)
Aldosterone antagonist				
1 month	14.4 (13.2,15.6)	13.1 (12.2,14.0)	11.7 (11.1,12.3)	11.0 (10.5,11.6)
3 months	21.6 (20.2,23.0)	20.2 (19.2,21.3)	17.8 (17.0,18.5)	17.1 (16.4,17.7)
6 months	24.5 (23.0,26.0)	23.4 (22.3,24.6)	21.0 (20.2,21.9)	20.1 (19.3,20.8)
1 year	27.9 (26.3,29.4)	27.0 (25.8,28.3)	24.4 (23.5,25.3)	23.6 (22.8,24.4)
5 years	36.6 (34.7,38.5)	38.9 (37.3,40.6)	37.8 (36.5,39.1)	36.9 (35.5,38.2)
Digoxin				
1 month	8.7 (7.8, 9.7)	10.9 (10.1,11.8)	13.5 (12.8,14.1)	16.4 (15.8,17.1)
3 months	12.2 (11.1,13.4)	15.9 (14.9,16.8)	18.8 (18.1,19.6)	22.8 (22.1,23.5)
6 months	13.4 (12.2,14.6)	17.5 (16.4,18.5)	20.7 (19.9,21.5)	24.7 (24.0,25.5)
1 year	14.4 (13.2,15.6)	19.2 (18.1,20.2)	22.4 (21.6,23.3)	26.5 (25.7,27.3)
5 years	19.0 (17.5,20.5)	24.4 (23.1,25.7)	29.6 (28.5,30.7)	35.1 (33.8,36.4)

Chapter 6

Heart failure in young vs. older adults: Data from the Alberta Ministry of Health and Wellness database.

6.1 Introduction

HF is a major public health issue and predominantly affects the elderly.(166;208) A limited number of studies have examined the characteristics of younger patients (<60 years) with HF and their attendance at the outpatient clinic, presentation to the emergency department, or admission to hospital, as most registries only hold hospitalisation data. Therefore, most epidemiological studies rely on hospitalisation data to determine the incidence, prevalence, and mortality rates of patients with HF neglecting those managed in the outpatient or emergency departments. A better understanding of younger patients with HF in these settings will enable health services to allocate and utilize resources more effectively. Accurate studies of the characteristics and outcomes of heart failure in younger patients will allow us to inform these patients better with respect to their likely prognosis.

The province of Alberta, Canada, consists of approximately 4.1 million residents, whom all have free access to a public health system including inpatient, outpatient, and emergency room physician services.(209) Utilising data from the administrative health care databases maintained by the Alberta Ministry of Health, our aim was to examine the incidence, characteristics, and outcomes in young (40-59 years) and very young (<40 years) adults with HF.

6.2 Methods

6.2.1 Databases

The statistician linked four databases maintained by the Alberta Ministry of Health, which records all contacts with the publically funded health care system for every citizen in Alberta, Canada.(210;211) The four databases are: 1) the Discharge Abstract Database, which records information (e.g.: dates, responsible diagnosis and up to 24 other diagnoses, comorbidities, procedures, length of stay and discharge status) on all admissions; 2) the Ambulatory Care Database, which records all visits to hospital-based physician office or

emergency departments and includes up to six diagnosis fields; 3) the Physician Claims Database, which tracks all physicians' claims from outpatient services and records up to 3 diagnostic codes per encounter; 4) the Population Registry, which records all the basic demographic and geographic information of all 4.1 million citizens. Each patient has a unique personal identifier allowing linkage of patient information across the databases.

6.2.2 Study population – incident and prevalent HF

All patients over 20 years of age with a first hospitalisation with HF as principal diagnosis between 1st April 1999 and 31st March 2009 in Alberta, Canada were identified. Patients with a HF hospitalisation in the five preceding years were excluded. Patients with a first HF hospitalisation were stratified into 1) first hospitalisation *without* prior diagnosis of HF at outpatient clinic or emergency department, and 2) first hospitalisation *with* a prior diagnosis of HF at outpatient clinic or emergency department. The combined of these is the incidence of first hospitalisation for HF.

Patients were identified using the international classification of disease (ICD)-9 (428) and ICD-10 (I50) codes for HF. The specificity and sensitivity of HF coding within this registry has previously been validated and was 98.7% and 77.3%, respectively.(209;212) If patients have had multiple contacts with different health care facilities within 24 hours, we used a hierarchical method to define the location of index HF diagnosis (i.e. inpatient superseded those from emergency department, and these supersede those from the outpatient setting).(213)

Co-morbidities were identified by using ICD codes for secondary diagnoses during the first HF hospitalisation and from any hospital visits within one year prior to the first HF hospitalisation. Socioeconomic status was examined by assigning a median Statistics Canada neighbourhood household income in Canadian dollars to patients based on their recorded place of residence.

6.2.3 Variables and Outcomes

Patients based on their age at first HF hospitalisation were stratified into 5 age categories: 20-39, 40-59, 60-69, 70-79 and ≥80 years. The following variables and outcomes were examined: 1) Baseline characteristics (sex, ethnicity, co-morbidities, and socioeconomic status measured by median household income using census data.); 2) First hospitalisation rates for HF without any prior diagnosis of HF in emergency department or outpatient clinic by age categories; 3) Number of patients with a first hospitalisation for HF with a prior diagnosis of HF at the outpatient clinic or emergency department and time from diagnosis to first hospitalisation; 4) One-year outcomes (presentation to emergency department, any re-hospitalisation, cardiovascular re-hospitalisation, HF re-hospitalisation, and number of days spent in hospital) after first HF hospitalisation diagnosis; and 5) Unadjusted and adjusted in-hospital, 30-day, 1-year and 5-year case fatality.

6.2.4 Statistical analysis

Results are presented as means and standard deviations or medians and interquartile range for continuous variables and proportions for categorical variables. Variables were compared across age categories using ANOVA for continuous variables and Chi-square for categorical variables. Cox's proportional hazard models were used to estimate the hazard of younger age compared with the referent age category 60-69 years. The model was adjusted for age, comorbidities, deprivation, and year of admission. All test were two sided with a level of significance set at $P < 0.05$. Analyses were performed using SAS version 9.2.

6.3 Results

6.3.1 Baseline characteristics

72977 patients were identified at their first HF admission in the period between 1st April 1999 and 31st March 2009. Overall, 36711 (50.3%) were women, and 33675 (46.1%) had prevalent HF. Baseline characteristics are presented separately for those with incident HF (defined as patients without prior diagnosis of HF in an outpatient clinic or emergency department) (Table 6.1), and those with prevalent HF (defined as a prior HF diagnosis in an outpatient clinic or emergency department in the period from 1st April 1994 until the first HF hospitalisation (Table 6.2).

Among patients with first hospitalisation *without* prior diagnosis of HF at outpatient clinic or emergency department, younger patients had fewer co-morbidities (Table 6.1). Younger patients had lower proportion of atrial fibrillation, hypertension, and peripheral arterial disease. The proportions of patients with prior MI or revascularisation were lowest in the patients aged 20-39 years and increased with age up to 60-69 years. Congenital heart disease was most prevalent in age group 20-39 years especially in men. Among patients <60 years, women had higher proportions of chronic obstructive pulmonary disease and malignant disease compared to men.

Similarly, among patients with first hospitalisation *with* prior diagnosis of HF at outpatient clinic or emergency department, younger patients had fewer co-morbidities (Table 2). Patients aged 20-39 years had the lowest proportions of previous MI or revascularisation. These proportions peaked at age group 60-69 years and decreased after. Younger (<60 years) patients had higher proportions of asthma and congenital heart disease. Renal failure was most prevalent in women aged 20-39 years, but least prevalent in younger men. Among patients aged <60 years, women had higher proportions of malignant disease, diabetes mellitus, and congenital heart disease compared to men.

6.3.2 Incidence of first hospitalisation with HF

The incidence rates of HF hospitalisations in both men and women declined from 1999 to 2008 (Figure 6.1). With the exception of the age group 20-39 years, the incidence of HF was higher in men than in women.

Table 6.1. Baseline characteristics of patients with first HF hospitalisation **without** a prior diagnosis of HF in either the emergency department or outpatient clinic by age categories

	Age									
	20-39		40-59		60-69		70-79		≥80	
N (%)	M	F	M	F	M	F	M	F	M	F
	310 (49.5)	316 (50.5)	3050 (62.3)	1849 (37.7)	3772 (58.9)	2631 (41.1)	6011 (52.7)	5406 (47.4)	6435 (40.3)	9522 (59.7)
Co-morbidities										
Prior MI	22 (7.1)	17 (5.4)	967 (31.7)	296 (16.0)	1264 (33.5)	531 (20.2)	1839 (30.6)	1108 (20.5)	1543 (24.0)	1606 (16.9)
Prior revascularisation	13 (4.2)	7 (2.2)	605 (19.8)	149 (8.1)	616 (16.3)	233 (8.9)	754 (12.5)	385 (7.1)	272 (4.2)	217 (2.3)
AF	42 (13.6)	13 (4.1)	667 (21.9)	235 (12.7)	1074 (28.5)	553 (21.0)	2076 (34.5)	1672 (30.9)	2271 (35.3)	3336 (35.0)
Hypercholesterolemia	5 (1.6)	4 (1.3)	316 (10.4)	129 (7.0)	413 (11.0)	235 (8.9)	480 (8.0)	389 (7.2)	238 (3.7)	303 (3.2)
Hypertension	106 (34.2)	77 (24.4)	1717 (56.3)	922 (49.9)	2390 (63.4)	1711 (65.0)	3960 (65.9)	3923 (72.6)	3888 (60.4)	6718 (70.6)
CVD	11 (3.6)	17 (5.4)	199 (6.5)	131 (7.1)	425 (11.3)	257 (9.8)	929 (15.5)	733 (13.6)	1148 (17.8)	1550 (16.3)
Diabetes mellitus	51 (16.5)	56 (17.7)	999 (32.8)	596 (32.2)	1385 (36.7)	970 (36.9)	1998 (33.2)	1723 (31.9)	1620 (25.2)	1943 (20.4)
Malignant disease	10 (3.2)	15 (4.8)	180 (5.9)	210 (11.4)	443 (11.7)	368 (14.0)	1121 (18.7)	698 (12.9)	1256 (19.5)	961 (10.1)
PAD	15 (4.8)	7 (2.2)	249 (8.2)	137 (7.4)	568 (15.1)	273 (10.4)	1051 (17.5)	686 (12.7)	1011 (15.7)	950 (10.0)
Renal failure	52 (16.8)	34 (10.8)	385 (12.6)	216 (11.7)	518 (13.7)	324 (12.3)	1028 (17.1)	727 (13.5)	1349 (21.0)	1295 (13.6)
COPD	58 (18.7)	88 (27.9)	845 (27.7)	707 (38.2)	1544 (40.9)	1190 (45.2)	2657 (44.2)	2150 (39.8)	2618 (40.7)	2874 (30.2)
Asthma	30 (9.7)	54 (17.1)	256 (8.4)	349 (18.9)	325 (8.6)	385 (14.6)	517 (8.6)	567 (10.5)	405 (6.3)	613 (6.4)
Congenital heart disease	43 (13.9)	25 (7.9)	96 (3.2)	60 (3.2)	57 (1.5)	45 (1.7)	74 (1.2)	66 (1.2)	45 (0.7)	54 (0.6)
Household income, Canadian dollars										
Median (IQR)	56073 (41872, 76076)	55018 (41696, 76231)	56067 (42390, 75483)	53654 (40026, 71766)	54479 (41735, 73334)	52831 (40713, 70980)	53436 (41686, 72125)	51984 (40472, 70833)	51725 (40472, 70668)	51189 (40038, 71675)

AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease; CVD= cerebrovascular disease; IQR=inter-quartile range; MI=myocardial infarction; PAD=peripheral arterial disease

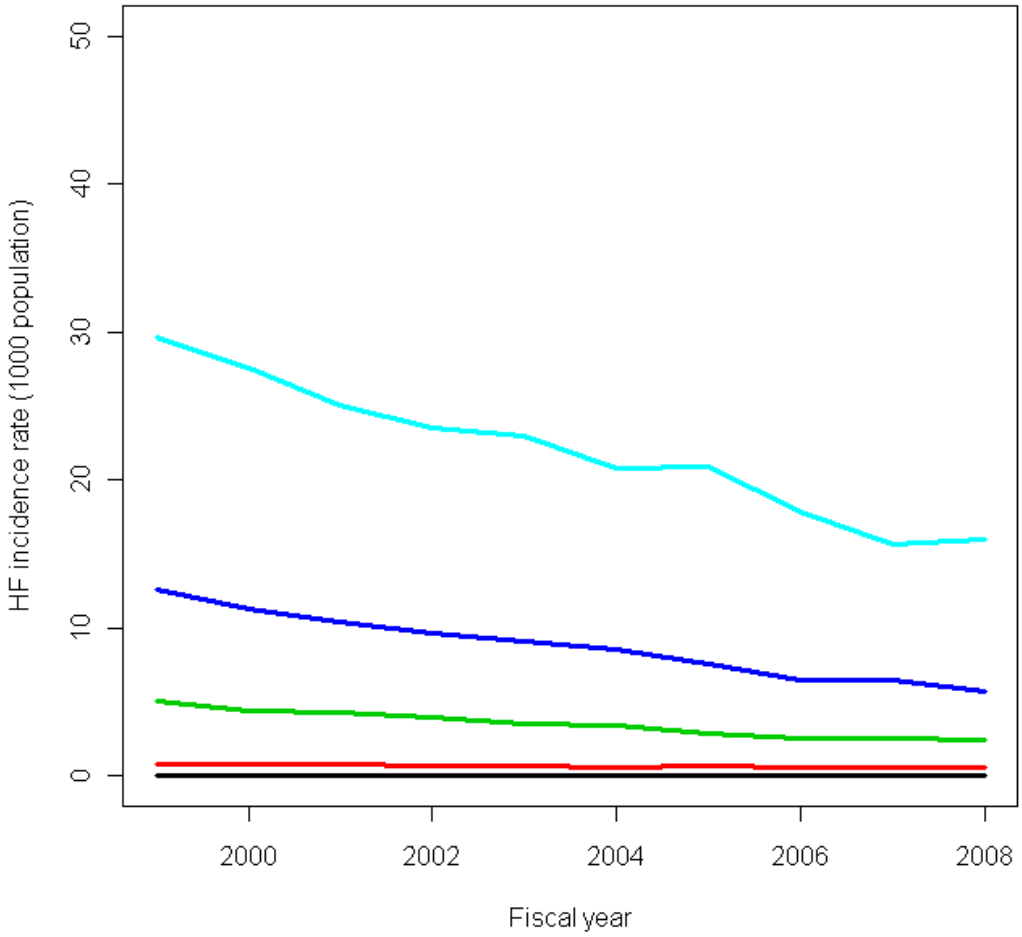
Table 6.2 Baseline characteristics of patients with first HF hospitalisation **with** a prior diagnosis of HF in either the outpatient clinic or emergency department by age categories

	Age									
	20-39		40-59		60-69		70-79		≥80	
N (%)	M	F	M	F	M	F	M	F	M	F
	79 (54.9)	65 (45.1)	1262 (60.4)	826 (39.6)	2521 (60.3)	402 (24.2)	5548 (55.5)	4445 (44.5)	7278 (42.1)	9992 (57.9)
Co-morbidities										
Prior MI	11 (13.9)	6 (9.2)	410 (32.5)	167 (20.2)	938 (37.2)	402 (24.2)	1935 (34.9)	1115 (25.1)	1902 (26.1)	1927 (19.3)
Prior revascularisation	1 (1.3)	0 (0.0)	116 (9.2)	37 (4.5)	213 (8.5)	79 (4.8)	354 (6.4)	166 (3.7)	141 (1.9)	110 (1.1)
AF	13 (16.5)	10 (15.4)	368 (29.2)	168 (20.3)	876 (34.8)	502 (30.3)	2348 (42.3)	1645 (37.0)	3049 (41.9)	4196 (42.0)
Hypercholesterolemia	1 (1.3)	4 (6.2)	132 (10.5)	52 (6.3)	263 (10.4)	136 (8.2)	404 (7.3)	278 (6.3)	242 (3.3)	284 (2.8)
Hypertension	26 (32.9)	20 (30.8)	799 (63.3)	536 (64.9)	1746 (69.3)	1212 (73.1)	3823 (68.9)	3227 (72.6)	4518 (62.1)	7039 (70.5)
CVD	4 (5.1)	4 (6.2)	102 (8.1)	84 (10.2)	272 (10.8)	186 (11.2)	879 (15.8)	633 (14.2)	1291 (17.7)	1659 (16.6)
Diabetes mellitus	11 (13.9)	18 (27.7)	513 (40.7)	349 (42.3)	1181 (46.9)	745 (44.9)	2127 (38.3)	1653 (37.2)	1830 (25.1)	2223 (22.3)
Malignant disease	2 (2.5)	3 (4.6)	55 (4.4)	59 (7.1)	281 (11.2)	168 (10.1)	833 (15.0)	437 (9.8)	1311 (18.0)	855 (8.6)
PAD	2 (2.5)	7 (10.8)	144 (11.4)	70 (8.5)	423 (16.8)	206 (12.4)	1008 (18.2)	532 (12.0)	1127 (15.5)	1033 (10.3)
Renal failure	11 (13.9)	18 (27.7)	223 (17.7)	155 (18.8)	509 (20.2)	290 (17.5)	1270 (22.9)	766 (17.2)	1698 (23.3)	1641 (16.4)
COPD	25 (31.7)	17 (26.2)	502 (39.8)	415 (50.2)	1303 (51.7)	857 (51.7)	2882 (52.0)	2189 (49.3)	3602 (49.5)	3670 (36.7)
Asthma	15 (19.0)	10 (15.4)	175 (13.9)	200 (24.2)	340 (13.5)	298 (18.0)	650 (11.7)	672 (15.1)	621 (8.5)	885 (8.9)
Congenital heart disease	14 (17.7)	20 (30.8)	51 (4.0)	45 (5.5)	58 (2.3)	49 (3.0)	69 (1.2)	59 (1.3)	52 (0.7)	66 (0.7)
Household income, Canadian dollars										
Median (IQR)	51889 (40078, 69714)	56469 (42848, 82840)	53881 (41251, 72125)	53619 (40472, 71436)	54159 (41096, 72235)	51598 (39716, 69513)	52788 (41442, 70658)	50803 (40322, 69746)	50645 (40042, 67933)	49725 (39168, 67670)

AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease; CVD= cerebrovascular disease; IQR=inter-quartile range; MI=myocardial infarction; PAD=peripheral arterial disease

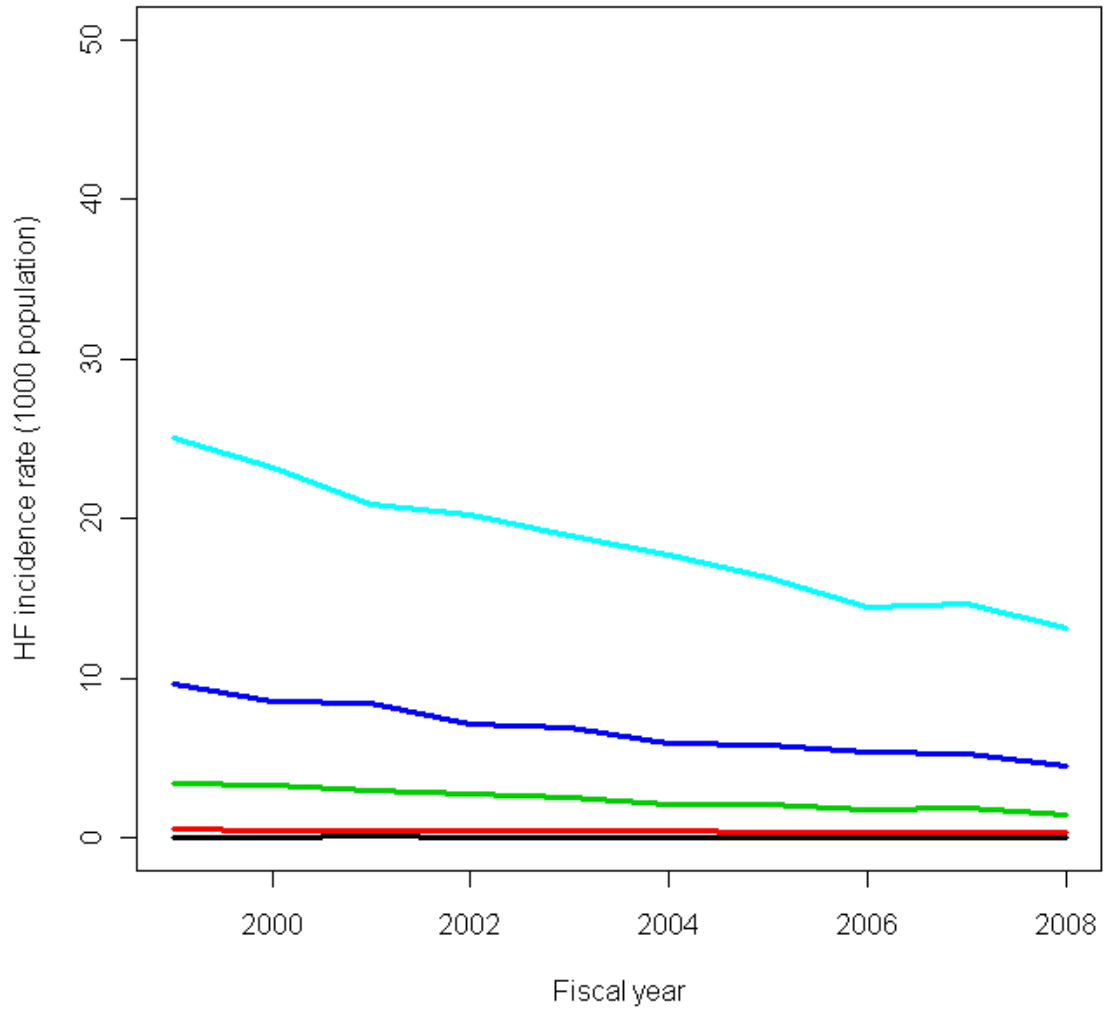
Figure 6.1. Incidence (per 1000 population) of first hospitalisation for HF **without** a prior diagnosis of HF in either the emergency department or outpatient clinic stratified by age for a) Men b) Women

a) Men



Age	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	p value
20-39	0.08	0.07	0.06	0.06	0.05	0.05	0.08	0.07	0.05	0.04	0.04
40-59	0.80	0.77	0.84	0.66	0.71	0.57	0.67	0.54	0.53	0.55	<0.0001
60-69	5.08	4.41	4.30	3.95	3.57	3.45	2.86	2.56	2.59	2.40	<0.0001
70-79	12.55	11.24	10.42	9.68	9.04	8.58	7.61	6.50	6.52	5.75	<0.0001
≥80	29.67	27.57	25.04	23.56	22.97	20.84	20.91	17.81	15.60	16.00	<0.0001

b) Women



Age	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	p value
20-39	0.07	0.08	0.09	0.08	0.05	0.07	0.05	0.06	0.05	0.06	0.02
40-59	0.53	0.48	0.46	0.44	0.49	0.42	0.36	0.34	0.35	0.32	<0.0001
60-69	3.38	3.33	2.97	2.71	2.56	2.07	2.07	1.82	1.83	1.45	<0.0001
70-79	9.61	8.50	8.47	7.11	6.91	5.89	5.83	5.43	5.29	4.50	<0.0001
≥80	25.01	23.18	20.93	20.21	18.90	17.77	16.25	14.48	14.67	13.17	<0.0001

6.3.3 Time from diagnosis of HF at outpatient clinic or emergency department to first hospitalisation with HF

Younger patients with a prior diagnosis of HF at outpatient clinic or emergency department were admitted to hospital with first HF hospitalisation sooner than older age group; median duration: 20-39 vs. ≥80 years: 401 vs. 1311 days in men, and 776 vs. 1435 days in women (Table 6.3).

Table 6.3. Time from a prior diagnosis of HF in either the outpatient clinic or emergency department to first hospitalisation for HF

	Age									
	20-39		40-59		60-69		70-79		≥80	
	M	F	M	F	M	F	M	F	M	F
Duration, mean (SD)	997.1 (1288.8)	1164.2 (1099.6)	1086.7 (1102.3)	1223.0 (1193.2)	1227.4 (1115.9)	1299.2 (1158.7)	1367.1 (1124.5)	1391.0 (1135.4)	1447.7 (1140.4)	1563.4 (1161.4)
Duration, median (IQR)	401 (93, 1565)	776 (269, 1746)	749 (157, 1753)	824 (220, 1957)	962 (257, 1923)	1045 (265, 2022)	1180 (400, 2076)	1223 (399, 2104)	1311 (511, 2189)	1435 (578, 2309)

IQR=inter-quartile range; SD=standard deviation

6.3.4 One-year outcomes after first HF hospitalisation

Patients aged 20-39 years had the highest emergency department visit within a year of first hospitalisation for HF compared to old age group (Table 6.4). However, the proportions of all cause, cardiovascular, or HF related hospitalisation were lower in patients aged 20-39 years.

Table 6.4. One-year non-fatal outcomes by age categories in patients hospitalised with HF

N (%) or median (IQR)	Age									
	20-39		40-59		60-69		70-79		≥80	
	M	F	M	F	M	F	M	F	M	F
Any ED visit	242 (62.2)	243 (63.8)	2477 (57.4)	1700 (63.6)	3776 (60.0)	2638 (61.5)	6789 (58.7)	5854 (59.4)	7594 (55.4)	10885 (55.8)
Any re-hospitalisation	158 (40.6)	152 (39.9)	1777 (41.2)	1269 (47.4)	2933 (46.6)	2029 (47.3)	5536 (47.9)	4632 (47.0)	6217 (45.3)	8636 (44.3)
CV re-hospitalisation	130 (33.4)	117 (30.2)	1577 (36.6)	1047 (39.1)	2643 (42.0)	1750 (40.8)	5032 (43.5)	4168 (42.3)	5638 (41.1)	7844 (40.2)
HF re-hospitalisation	67 (17.2)	62 (16.3)	852 (19.8)	549 (20.5)	1580 (25.1)	1048 (24.4)	3214 (27.8)	2736 (27.8)	3994 (29.1)	5570 (28.5)

CV=cardiovascular; ED=emergency department; HF=heart failure; IQR=interquartile range.

6.3.5 Mortality rate at 30 days, 1 year, and 5 years

The youngest age group had the lowest 30 days, 1 and 5 year mortality rates (Table 6.5). Of those who died within a year from their HF hospitalisation, approximately half of the deaths occurred within 30 days of HF hospitalisation. The adjusted case fatality ratios remained lowest in the youngest age group (Table 6.6). Younger men (<60 years) had a lower hazard ratio (HR) for all cause mortality compared to women of the same age category.

Table 6.5. Case fatality stratified by age categories after first hospitalisation with HF between 1999 and 2009 a) 30 days, b) 1 year, and c) 5 years

a) 30 days

N (%)	Age									
	20-39		40-59		60-69		70-79		≥80	
	M	F	M	F	M	F	M	F	M	F
	389 (50.5)	381 (49.5)	4312 (61.7)	2675 (38.3)	6293 (59.5)	4290 (40.5)	11559 (54.0)	9851 (46.0)	13713 (41.3)	19514 (58.7)
Thirty day death	26 (6.7)	40 (10.5)	353 (8.2)	262 (9.8)	717 (11.4)	491 (11.5)	1931 (16.7)	1387 (14.1)	3470 (25.3)	3890 (19.9)

b) 1 year

N (%)	Age									
	20-39		40-59		60-69		70-79		≥80	
	M	F	M	F	M	F	M	F	M	F
	382 (50.8)	370 (49.2)	4210 (61.7)	2609 (38.3)	6172 (59.5)	4199 (40.5)	11360 (54.0)	9690 (46.0)	13374 (41.2)	19085 (58.8)
One year death	50 (13.1)	60 (16.2)	631 (15.0)	460 (17.6)	1312 (21.3)	880 (21.0)	3550 (31.3)	2506 (25.9)	6018 (45.0)	7019 (36.8)

c) 5 years

N (%)	Age									
	20-39		40-59		60-69		70-79		≥80	
	M	F	M	F	M	F	M	F	M	F
	222 (47.8)	242 (52.2)	2616 (61.5)	1638 (38.5)	4092 (59.5)	2791 (40.6)	7733 (53.7)	6661 (46.3)	8642 (40.8)	12545 (59.2)
Five year death	60 (27.0)	76 (31.4)	795 (30.4)	556 (33.9)	1904 (46.5)	1186 (42.5)	4813 (62.2)	3594 (54.0)	7047 (81.5)	9270 (73.9)

Table 6.6. Adjusted Case Fatality (Multivariable analysis adjusted for comorbidities, income, and year of admission)

	Adjusted Case Fatality, OR (95% CI)					
	30 Day		1 Year		5 Years	
Age	Men	Women	Men	Women	Men	Women
20-39	0.56 (0.37, 0.84)	0.90 (0.64, 1.28)	0.60 (0.44, 0.82)	0.77 (0.57, 1.04)	0.51 (0.37, 0.70)	0.69 (0.51, 0.92)
40-59	0.74 (0.65, 0.85)	0.85 (0.72, 1.00)	0.73 (0.65, 0.81)	0.83 (0.73, 0.95)	0.59 (0.53, 0.65)	0.71 (0.62, 0.81)
60-69	1	1	1	1	1	1
70-79	1.43 (1.31, 1.58)	1.28 (1.14, 1.43)	1.54 (1.43, 1.66)	1.33 (1.22, 1.46)	1.70 (1.57, 1.84)	1.59 (1.44, 1.74)
≥80	2.31 (2.11, 2.53)	2.00 (1.80, 2.22)	2.64 (2.46, 2.84)	2.32 (2.01, 2.29)	4.43 (4.07, 4.83)	3.99 (3.65, 4.37)

6.4 Discussion

In this cohort study, utilising the linked health registers of Alberta, Canada, younger patients with HF differed from the elderly HF patients in a number of ways including comorbidity burden, incidence of first hospitalisation, and fatal and non-fatal outcomes.

Younger patients with HF had less comorbidity. In patients with prevalent HF, time from diagnosis of HF at outpatient clinic or emergency department to first HF hospitalisation were markedly shorter in younger compared to older patients. Perhaps not surprisingly, younger patients have lower mortality.

6.4.1 Incidence of HF

The incidence of HF is declining from 1999 to 2008 in all age categories albeit to a lesser degree in patients aged 20-39 years. The is consistent with recent data from the Olmsted County, Minnesota, demonstrating age- and sex-adjusted incidence of HF declined from 315.8 per 100 000 in 2000 to 219.3 per 100 000 in 2010.(214) This improvement may reflect the declining incidence of myocardial infarction,(215;216) the greater awareness and better treatment of hypertension,(217) and the improving outcomes for patients with diabetes.(218)

6.4.2 Hospitalisations

After presenting to outpatient clinic or emergency department with a diagnosis of HF, patients aged 20-39 years were admitted to hospital much sooner than older patients. The Alberta dataset are unique as it allows the linkage of hospitalisation data with outpatient clinic and emergency department data making it possible to determine time from initial diagnosis anywhere in the health care system until first hospitalisation for HF. There

might be a few plausible explanations to this. Younger patients have different aetiology of HF and some of these might be more severe.(199;219) In our study, the youngest age group had the highest prevalence of congenital heart disease. Certain mutations such as dystrophin defects are more prevalent in younger men and others such as mutations in cardiac troponin T or cardiac β-myosin heavy chain resulted in early onset ventricular dysfunction and HF in patients with DCM.(185-187) X-linked laminopathies and dystrophin defect may have played a role.(183;184) In other cohorts, ejection fraction is lowest in younger patients (I do not have information on EF in this study), which might have prompted physicians to admit them.(199;219) Unlike older patients who might be more readily attributing their HF symptoms and functional limitation to age, younger patients with higher societal and family demands might be more likely to seek help.

After discharge from first HF hospitalisation, younger patients were more likely to present to emergency department but less likely to be re-hospitalised for all cause, CV or HF. This could partly be explained by the lack of classical clinical and radiological signs of HF in younger patients with HF.(199) Younger patients are less likely to have peripheral oedema, pulmonary rales, and radiological evidence of pulmonary oedema.(199) Physicians managing younger patients in emergency department may have been reassured by the absence of these classical HF signs and symptoms and discharged patients. Conversely, younger patients with decompensated HF have fewer comorbidities and likely to exhibit less frailty. Physicians managing them may felt appropriate to manage them as an outpatient.

6.4.3 Mortality

Younger patients have lower mortality in both men and women. Compared to the 60-69 years age group, the correlation between younger age and mortality was stronger in men. The observed mortality rates are comparable to previous HF epidemiological studies.(12;17;67) However, it might be more reasonable to compare their outcomes to their peers rather than older patients. Comparing to the age-sex specific mortality rates in the general populations in Alberta, Canada, younger patients have the highest standardized mortality ratio, hence depicting a greater relative risk compared to older patients with HF.

In our study, men aged <60 years had a lower mortality rate compared to women aged <60 years, which is contrary to previous studies that has reported worse survival in men with HF.(220;221) A possible explanation could be the higher proportions of congenital heart disease and malignant disease in younger women in our data.

6.5 Limitations

Although use of the linked administrative datasets in Alberta means that we could capture all interactions with the health care system and follow all patients over time, there are some limitations which warrant consideration. The diagnosis of HF was obtained from hospital administrative registries, therefore relies on the accuracy of patient records and the responsible physicians. However, the Alberta administrative data have been validated for patients with HF and for comorbidities. Data on ejection fraction, laboratory results, biomarkers, causes of HF, and prescribing data are lacking. The numbers of younger patients are small; hence, there are greater uncertainties of the results.

6.6 Conclusions

Comparing to older patients, younger adults with HF were admitted to hospital for HF sooner after a diagnosis of HF at the emergency department or the outpatient clinics and were also more likely to be diagnosed with HF for the first time in the hospital rather than as an outpatient. After first HF hospitalisation, younger patients were more likely to present to emergency department but less likely to be re-hospitalised. Mortality rates in younger adults with HF were low.

Chapter 7

Final discussion

In this thesis, I have examined the clinical characteristics and outcomes of younger adults with HF in 4 different populations: a randomised clinical trial, a meta-analysis, a primary care database, and a hospital administrative database. Compared with older patients, younger patients with HF have a different clinical profile, including a different pattern of symptoms and signs, aetiology, comorbidities, treatments, more hospitalisations and a better survival.

Very little has been published previously on the symptoms and signs of HF in younger patients with HF. In the CHARM programme, a third heart sound and hepatomegaly were more commonly found in younger adults compared to older patients. However, peripheral oedema and pulmonary crackles were less common in younger adults. Chest radiographic findings were congruent with these findings, with abnormalities such as pulmonary oedema or pleural effusion being much less common in younger adults. Similarly, during acute episode of decompensated HF requiring hospitalisation, clinical pulmonary oedema and radiological signs of heart failure were less common in younger adults. These differences in clinical and radiological findings in younger adults with HF can easily mislead physicians and delay diagnosis when faced with a younger patient with breathlessness. These findings are novel and unique to this dataset owing to the detail documentation of symptoms and signs and radiological findings in a randomised trial compared to other dataset.

The aetiology of HF in younger adults <40 years has previously been ill-defined. In both CHARM and MAGGIC, dilated cardiomyopathy was the most common aetiology of HF in younger adults aged <40 years. In both of these studies, the aetiology of HF was investigator reported, without systematic pre-specified assessments.

As may be expected, younger patients have fewer cardiovascular comorbidities (ischaemic heart disease, previous myocardial infarction, hypertension, stroke, diabetes, atrial fibrillation, percutaneous coronary intervention and coronary artery bypass grafting), findings which are consistent in all four datasets. However, compared to older patients, the proportions of asthma and depression were higher in younger adults in the CPRD. Almost a quarter to a third of patients aged 20-29 and 30-39 years had a diagnosis of asthma or

depression at index HF diagnosis. Similarly, in the Alberta database, younger patients aged 20-39 had a higher proportion of asthma at index HF hospitalisation compared to older patients. It is not clear why this should be the case. Depression is known to be prevalent among patients with HF. Younger patients with HF have worse health related quality of life. This is possibly explained by the greater disparity between their functional status and expectations. The demands from employment and family, and the financial burden resulted from ill health must play a major role. Similarly, the proportion of asthma in younger adults with HF is intriguing. The relationship with inhaled beta-agonists may have contributed as discussed in Chapter 5. Or younger adults who initially presented to primary care with breathlessness may have been mis-diagnosed as asthma initially. Further studies examining the relationship between HF and asthma or depression will be very informative.

Younger adults were more likely to receive HF medications in both CHARM and MAGGIC. Comparing to older patients, younger adults have more severe left ventricular dysfunction, and a greater proportion with HF-REF, mandating treatments with ACE inhibitor or ARB, beta-blocker, and spironolactone. Younger adults with better renal function may tolerate these medications better. However, patients recruited into clinical trials are closely monitored and medications optimally titrated. 'Real-life' populations are very different. In the CPRD, the prescription rates for ACE inhibitor or ARB, beta-blocker, and mineralocorticoid receptor antagonist in patient aged 20-29 years were the lowest at 1 year after index HF diagnosis. Worse still, the initiations for these medications were slow in patients aged 20-29 years. Perhaps optimisation was limited by comorbidities such as the use of beta-blockers in patients with asthma. Alternatively, physicians managing younger adults with HF may be complacent and reassured by their better NYHA functional class and survival.

This thesis advances our understanding of the reasons for HF hospitalisation and clinical presentation during decompensation in younger patients. The large datasets including a randomised trial and linked hospital, outpatient and emergency department administrative databases permit more detail examination of the circumstances leading to HF hospitalisations, and allow comparisons between age groups. In CHARM, younger adults were less likely to comply with medications, dietary restriction, and alcohol intake leading to their hospitalisation for HF. As discussed previously, younger adults with HF

were less likely to present with clinical pulmonary oedema or radiological signs of HF during decompensated HF. In the Alberta Ministry of Health database, by linking hospitalisation data with outpatient clinic or emergency department, the duration from the first diagnosis of HF at outpatient setting to the first HF hospitalisation can be determined. Compared to older patients, younger adults aged <40 years were admitted to hospital with HF much sooner after their first HF diagnosis at outpatients clinic or emergency department. It is plausible that younger adults with a new diagnosis of HF may be struggling to adhere to their medications and lifestyle restriction, leading to earlier hospitalisation with HF. Conversely, it could also be explained by the lower prescription rates of HF medications in younger adults aged 20-29 years as discussed in the CPRD analysis. In the Alberta database, younger adults <40 years were also more likely to present to the emergency department following their index HF hospitalisation. Intriguingly, this did not lead to a higher proportion of hospitalisation.

Short and long-term mortality rates in younger adults are lower compared to older patients. In CHARM and MAGGIC, younger adults had lower 3-year mortality compared to older patients which was comparable between the two datasets. In the CPRD analysis, between 1988 and 2011, mortality rates in patients with HF have been improving. Mortality rates in younger men aged 20-29 and 30-39 years have reduced by almost 80%. Similarly, in the Alberta database, mortality rates in younger adults following first HF hospitalisation are lower compared to older patients. These findings concurred with a recent Swedish study examining mortality trends between 1987 and 2006, which showed decreasing case fatality in younger patients by more than 50%, but a plateau since 2001.(17) In contrast, the CPRD followed up patients from 1988 to 2011 showing that the mortality continued to improve after 2006. This may reflect the wider use of mineralocorticoid receptor antagonist and cardiac resynchronisation therapy following publication of landmark trials in the last decade. Younger adults, although having lower mortality rates compared to older patients, are more likely to compare themselves to their peers. Calculating the standardised mortality ratio comparing the studied population (i.e. young adults with HF) to sex and age matched general population may be a better method to reflect the substantial risk of death in younger adults with HF comparing with their peers.

Very little information exists regarding the incidence of HF in younger adults and even less so on its trend over time.(17;30) In the Alberta database, the incidence of first HF hospitalisation declined between 1999 and 2008 for all age groups. This is consistent with recent publications from Minnesota and Scotland.(67;214) However, a Swedish study utilising the national hospital discharge registry reported an increase in first HF hospitalisation by 50% and 43% between 1987 and 2006 in patients aged 18-34 and 35-44 years, respectively.(17). The authors postulated that an increase in incidence of cardiomyopathy in younger patients might play a part, or that physicians were more likely to admit younger patients for further investigations. In the Alberta database, the majority (99%) of admissions were emergency. Therefore, the incidence of HF hospitalisation had fewer patients admitted for investigations. The study from Minnesota included only patients with validated HF using the Framingham Study criteria. The differences in incidence between these databases might partly be explained by the different inclusion of different cohort of patients with HF (emergency vs. emergency and elective admission and validated HF vs. coding).

The strength of this thesis is that it consists of 4 large databases representing 4 different HF populations (a randomised clinical trial, a meta-analysis, a primary care database, and a secondary care database) allowing detailed examination of younger adults with HF from different perspectives. I was also able to substantiate findings from the UK with data from Alberta, Canada. Specific limitations have been discussed in each chapter, but some further general limitations warrant consideration. The primary and secondary care databases included in this thesis are from North America and the UK. These findings might not apply to other developed countries. Similarly, these findings might also be very different from younger adults with HF from other developing countries. Although all 4 databases complimented each other in many ways, there also represent 4 very different HF populations including different variables limiting the ability to corroborate some of the finding across all the datasets.

Future research should focus on establishing the aetiology of HF in younger adults, especially those <40 years. Better understanding of the causes of HF in younger adults is key to early diagnosis and management. It might even help to further develop therapeutic options. The difference in symptoms and signs of HF and the circumstances leading to HF

hospitalisation in younger adults need to be validated in other cohorts. More epidemiological study using linked primary and secondary care datasets would provide greater definition of the incidence and prevalence of younger adults with HF in these populations, and also examine how younger adults interact with and transition between primary and secondary care.

Lastly, over the course of preparing this thesis, it is increasingly clear that the definition of young is fluid. Very young adults <40 years have different baseline characteristics as described above compared to older patients Mortality rate, however, did not differ much among young adults <60 years. Perhaps not surprisingly, with increasing age, the number of co-morbidities increases with higher mortality rate.

I hope this thesis has successfully summarised and extended our current understanding of young adults with HF. Some of the questions have been answered but many more are still to be addressed. This provides a basis for further research in young adults with HF.

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